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SYPHILIS OF TENDON OF LONG HEAD OF BICEPS MUSCLE AND OF OLECRANON BURSA

V. L. SCHRAGER, M.D.
CHICAGO

GENERAL CONSIDERATIONS

The long head of the biceps muscle is vulnerable and receptive to both specific and nonspecific infections. This vulnerability is based on a number of factors.

Anatomic Factors.—The long head of the biceps muscle is inserted into the supraglenoid tuberosity and the glenoid ligament by a long tendon (9 cm.), which glides over the head of the humerus, within the capsule of the joint. It is invested with a synovial sheath, which is an evagination of the capsule, and then slides down the bicipital groove. This bursa is closed at its lower end and is 5 cm. long. Codman [1] stated: "To my mind it is more properly called a sheath, but is in fact merely an extension of the joint cavity with which it freely communicates."

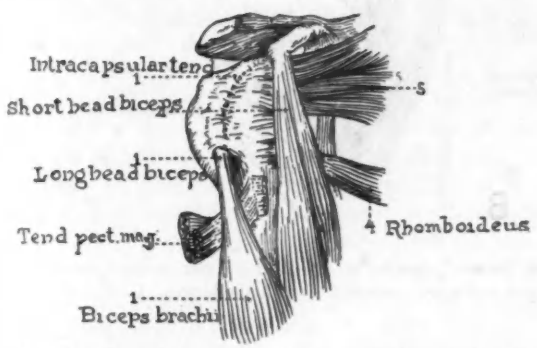

Fig. 1.—Long head of the biceps muscle entering the capsule of the shoulder joint (from Testut, L.: Traité d'anatomie humaine, Paris, Gaston Doin, 1928-1931).

Constant movement of the tendon in a rather shallow groove and relative instability of the shoulder make it possible for the tendon to be injured and to dislocate itself out of the groove. A. W. Meyer, of Stanford University,[2] dissecting 1,000 shoulders in cadavers, found 50 examples of marked dislocation of the tendon and many others of dislocation of lesser degree.

Physiologic Factors.—Although the tendon has several functions in the dynamics of the shoulder, it is not entirely indispensable, since the same functions are assisted, duplicated or supplemented by other muscles or tendons. Nevertheless, the physiologic assignments of the tendon are multiple, and it participates strenuously in many of the activities of the shoulder.

Pathologic Factors.—The long head of the biceps muscle is a vestigial structure. Meyer [2] spoke of attrition of its head and of structures in its vicinity. In the course of his numerous dissections he found thinning, fraying and fibrillation. He also encountered destruction and separation of its ends with the obtainment of new tendinous attachments. He spoke of long-continued overuse in positions of abduction and external rotation. Meyer's observations were subsequently confirmed by Horwitz,[3] who in the routine dissection of 150 shoulder joints in cadavers also found fraying, fibrillation and flattening of the tendon in 30 specimens. In 4 specimens complete tears were noted. Gilcreest [4] reported 100 cases of rupture of the long head of the biceps muscle. Constant friction against deposits resulting from arthritic infections in the bicipital groove explains various degrees of damage to the tendon.

The tendon may be the seat of rheumatic infections from a focal source; it may be invaded by colon or by dysentery bacilli (J. Pasteur [5]).

McKenna,[6] speaking of tendinitis of the long head of the biceps muscle, stated in his conclusions that there are atavistic changes during the middle decades of life, consisting of avascularity, fibrillation, saponification and calcification.

1. Codman, E. A.: The Shoulder, Boston, T. Todd Company, 1934.

2. Meyer, A. W.: Spontaneous Dislocation and Destruction of Tendon of Long Head of Biceps Brachii, Arch. Surg. **17**:493 (Sept.) 1928.

3. Horwitz, M. T.: Lesions of Supraspinatus Tendon and Associated Structures: Investigation of Comparable Lesions in Hip Joint, Arch. Surg. **38**:990 (June) 1939.

4. Gilcreest, E. L.: Rupture of Muscles and Tendons, Particularly Subcutaneous Rupture of Biceps Flexor Cubiti, J. A. M. A. **84**:1819 (June 13) 1925.

5. Pasteur, J.: J. de radiol. et d'électrol. **16**:419, 1932.

6. McKenna, D. E.: M. Times, New York **68**:359, 1940.

In April 1938, I [7] suggested that painful or "frozen" shoulder in the absence of an actual pathologic condition within the joint or bursas is due to tendosynovitis of the long head of the biceps muscle. What was then a mere clinical conjecture has just been proved to be a fact by Lippmann.[8] His pathologic material was obtained from 12 surgical cases of "frozen shoulder" and was appraised by Dr. Oppenheim, pathologist at the Mount Sinai Hospital of New York, who found various degrees of inflammation in all specimens.

It can thus be seen that anatomically, by virtue of its arrangement, this tendon is a somewhat handicapped one. Physiologically, the tendon is taxed beyond its physiologic assignments. Pathologically, it falls prey to various types of nonspecific and specific infections.

This is, then, the background of this vulnerable tendon, which places it in a status minoris resistentiae.

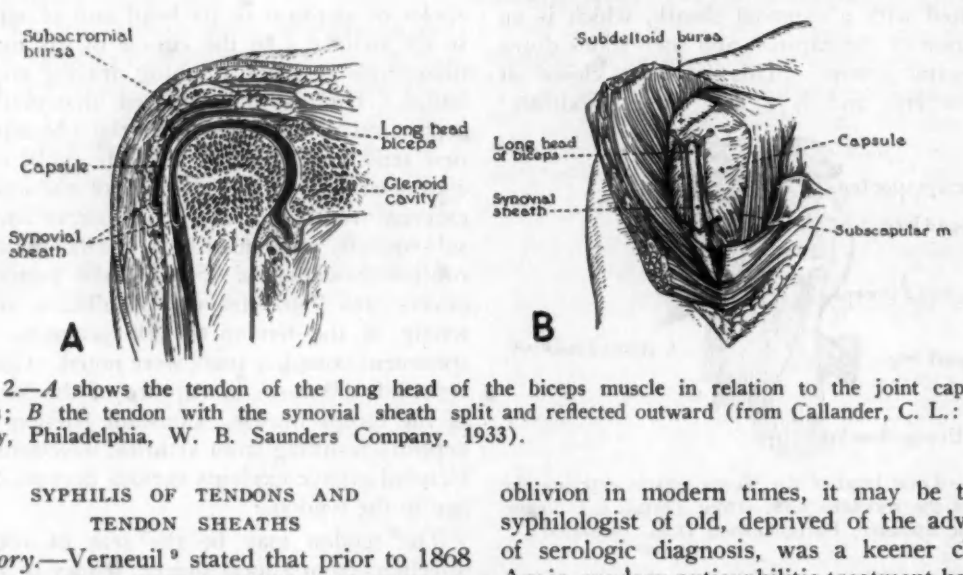

Fig. 2.—*A* shows the tendon of the long head of the biceps muscle in relation to the joint capsule and humerus; *B* the tendon with the synovial sheath split and reflected outward (from Callander, C. L.: Surgical Anatomy, Philadelphia, W. B. Saunders Company, 1933).

SYPHILIS OF TENDONS AND TENDON SHEATHS

History.—Verneuil [9] stated that prior to 1868 there was no mention of syphilis of tendons in the literature. He reported 4 cases of syphilitic "subacute exudate" in the tendon sheaths of extensor muscles of fingers; all the patients were women.

The French school of syphilologists, represented by Fournier, Velpeau, Lancereaux, Verneuil, Mauriac and others, reported a number of cases of syphilis of tendons. Finger,[10] Austrian syphilologist, published in 1884 an extensive article on syphilis of tendons and joints. Like Verneuil, he described acute and subacute exudate in the tendon sheaths of extensor muscles of fingers, especially in women. In Germany, Schuchardt [11] and Hölder [12] spoke of syphilis of tendons, the latter finding the condition more prevalent in muscles. In the United States, Keyes [13] mentioned the subject and reported several cases. Hektoen and Riesman [14] spoke of tendovaginitis acuta syphilitica occurring in secondary syphilis. Stokes,[15] on the other hand, stated that the involvement of tendon sheaths in early syphilis is rare.

The literature on syphilis of tendons seems to have been prolific in the seventies and eighties, especially in France, sporadic thereafter and seldom mentioned in modern literature on syphilis. While it is difficult to explain the discrepancy between the thorough knowledge of the subject in the seventies and eighties and the total oblivion in modern times, it may be that the syphilologist of old, deprived of the advantages of serologic diagnosis, was a keener clinician. Again, modern antisyphilitic treatment has either modified or obviated the pathologic changes of syphilis.

Etiology and Diagnosis.—The earliest diagnoses were established largely on therapeutic tests, some of the syphilitic tendinitis disappearing like magic on this treatment. Syphilis of tendons is seldom suspected, tendinitis being the

7. Schrager, V. L.: Surg., Gynec. & Obst. **66**:785, 1938.

8. Lippmann, R. K.: Frozen Shoulder: Periarthritis; Bicipital Tenosynovitis, Arch. Surg. **47**:283 (Sept.) 1943.

9. Verneuil: Gaz. hebd. de méd. **5**:609, 1869.

10. Finger, E. A.: Wien. med. Wchnschr. **34**:864, 890, 920, 944, 971, 993 and 1026, 1884; Lehrbuch der Haut- und Geschlechtskrankheiten, Leipzig, F. Deuticke, 1907.

11. Schuchardt, K.: Virchows Arch. f. path. Anat. **135**:394, 1894.

12. Hölder: Lehrbuch der venerischen Krankheiten, 1909, pp. 185 and 421.

13. Keyes, E. L., Jr.: Syphilis, New York, D. Appleton and Company, 1908.

14. Hektoen, L., and Riesman, D.: An American Text-Book of Pathology, Philadelphia, W. B. Saunders Company, 1901.

15. Stokes, J. H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1934, p. 687.

prevalent diagnosis for acute conditions and ganglion or tuberculosis for chronic conditions.

A history of syphilis, especially in untreated or inadequately treated patients, positive serologic reactions and characteristic scars on the forehead and the tibia are helpful in diagnosis. However, many untreated patients show a slightly positive and frequently a negative reaction.

The presence of a mass may suggest a tumor, as it did in the case to be described. However, tumors of the tendon sheaths are rare. Canavero[16] estimated that there are approximately 1 or 2 cases of such growths in every 2,000 admissions to hospitals and clinics. In the combined statistics of the Brooklyn Cancer Institute, the Cumberland Hospital and the Jewish Sanatorium and Hospital for Chronic Diseases, there were only 5 cases of tumor of the tendon sheath among 1,500 admissions to the hospitals and 150,000 admissions to the clinics. Coley and Pierson[17] collected 27 cases of tumor of the synovial sheath from the general literature.

Syphilitic tendinitis may be associated with painless swelling of joints, which is invariably diagnosed at first as being rheumatic or arthritic. The pain, if at all present, is more likely to be nocturnal and is often relieved by exercise. Fournier expressed the opinion that pains about the knee and elbow at the beginning of secondary syphilis are due to syphilis of tendons in the vicinity of joints. He stated that the pain at the bend of the elbow and the inability of the patient to extend the forearm are characteristic of secondary syphilis, and he designated the condition pseudorheumatism. Pains about the elbow of syphilitic origin may be referred to the tendon of the long head of the biceps.

The exudate may be either slightly painful or, more often, painless and as a rule does not affect function. There may be present thickening of the tendons and painless and movable nodules along their course. The overlying skin may either be normal or show inflammatory changes, sinuses, thickening or calcification.

Pathology.—One of the characteristics of syphilitic tendinitis is the presence of nodules in the tendons. Lisfranc[18] described white nodosities in tendons (*nodosités blanches*), which Lancereaux[19] ascribed to syphilis. They always are a tertiary manifestation, painless and movable. Schuchardt[11] reported a case in which a hazelnut-sized node in the long head of the biceps of a merchant with untreated syphilis responded well to antisyphilitic treatment. Lisfranc described "white tumor" in the achilles tendon of an opera dancer, which disappeared completely on the administration of potassium iodide.

Syphilis has a predilection for certain tendons. According to Lancereaux, thick and strong tendons are more often involved, such as those of the biceps and triceps surae muscles and the extensor muscles of fingers. Schuchardt reported syphilitic nodules in the tendon sheaths of the supinator longus, extensor carpi radialis and extensor pollicis longus muscles, all in female patients.

Many syphilologists have mentioned involvement of the tendon of the long head of the biceps muscle. Cases of such involvement have been reported by Fournier, Schuchardt and Lisfranc. Finger stated the belief that tendosynovitis of the tendon of the long head of the biceps muscle is characteristic of secondary syphilis and that the pain, if present, is always referred to the elbow.

Lancereaux spoke of plastic exudate, infiltration and thickening, as well as of gummas. Schuchardt found thickening of the inner sheath of tendons. He also found masses of lymphocytes, which he designated as miliary gummatous nodules and areas of necrosis, resembling caseous gummas of the testicle. There were present in the granulation tissue of the deeper layers of tendon sheaths giant cells with multiple nuclei, resembling those present in tuberculosis.

REPORT OF A CASE

History.—I. W., aged 61, retired, was a well built and well nourished man, looking a bit younger than his age. He had been in fair general health all his life. For the last twenty years, however, he had complained of pain in various joints, and he had been incapacitated for about twelve years. During that time he had had periodic large swellings in various joints, such as those of the shoulder, the wrist and the knee, which inconvenienced him because of the size of the swellings but not because of pain. He could get around well using a cane, or occasionally crutches, simply because they made walking a little easier. He consulted several physicians, who diagnosed his condition as either rheumatism or arthritis. During the last routine examination it was discovered that his blood showed a 4 plus Wassermann reaction. The attending physician gave him several injections of neoarsphenamine and bismuth. After the eighth treatment, a deep jaundice developed. The patient became alarmed, discontinued the treatment and visited the Mayo Clinic, in Rochester, Minn. There, a diagnosis of toxic hepatitis was made, and he was advised never again to take arsenicals for the treatment of syphilis. He had not had any antisyphilitic treatment since.

When I saw the patient he stated that about six weeks previously, while squeezing an orange, he experienced a rather sharp pain in the upper portion of the left arm.

16. Canavero, M.: Policlinico (sez. chir.) **41**:341 (July) 1934.

17. Coley, B. L., and Pierson, J. C.: Surgery **1**:113, 1917.

18. Lisfranc, J.: Gaz. d. hôp., 1842.

19. Lancereaux, E.: Traité historique et pratique de la syphilis, Paris, J.-B. Baillière & fils, 1866, p. 264; ed. 2, Paris, Germer-Baillière, 1873.

A couple of days later he noticed a swelling in that location, which was painless. This swelling progressed in size, and when I saw him, about a week later, he insisted that the tumor mass be removed.

Examination of the patient revealed that he had no organic disease and that he was in excellent condition for his age. There was a large swelling, elastic in character, in both knees, which were painless both to touch and pressure and on active and passive movement. The ankles were slightly swollen; there was some swelling in the left shoulder, which was the residual of a former, larger swelling. The routine laboratory tests gave normal results. As mentioned before, the original Kahn and Wassermann reactions were negative, but there was a 2 plus reaction with other methods. In the upper third of the right arm, on its anterior and lateral aspect, there was a tumor mass the shape of a large banana. It was somewhat soft, was painless and could be displaced laterally but not upward or downward. There was also a large, inflamed olecranon bursa, about the size of a large walnut, likewise painless and movable.

On the basis of the age of the patient, his reasonably good record of health, his healthy children and the fact that for a number of years he had had effusions

Fig. 3.—A tumor mass displacing the tendon and muscle laterally.

in various parts of the body, two tentative diagnoses were made: tumor of undetermined origin, or serous effusion in the tendon sheath of the long head of the biceps muscle. The olecranon bursitis was considered coincidental and not related to the tumor mass in the upper portion of the arm.

Operation and Findings.—With the area under anesthesia induced with solution of procaine hydrochloride, an incision was made in the upper third of the arm, laterally to the midline. The tumor mass was about 3 inches (7.5 cm.) in length and about 1½ inches (3.8 cm.) in width. It was located in the tendon sheath of the long head of the biceps muscle and, by its size, displaced the muscle laterally and internally.

The mass had a thin capsule of connective tissue. It was movable laterally, but it was attached to the deeper structures and could not be moved upward or downward and seemed to lose itself in the bicipital groove. Although the dissection was reasonably easy, for the most part, the capsule was perforated at two or three points. A yellowish mass, comparable to well cooked, mashed sweet potatoes, escaped through these rents. The mass was finally excised, sharp scissors being required to detach it from its lower and upper attachments. After the mass had been removed, the same kind of yellowish material escaped from the bicipital groove. It was evident that this mass and its contents were situated in the sheath of the tendon of the long head of the biceps muscle. The tendon itself did not look normal. Instead of being white and glistening, it was red in spots; instead of running straight upward, it bulged at one point. This bulge was made up by an almond-shaped mass, which was removed for diagnosis. It represented a node in the tendon and was movable. A few strips of the tendon and its sheath, which were red and frayed, were also removed for diagnosis.

An olecranon bursa the size of a large walnut was present over the right elbow. It had a thick capsule. The contents of the bursa were exactly like those found in the tendon sheath of the biceps muscle.

Both wounds healed by primary intention, and the patient left the hospital within four days. There was no subsequent evidence of lack of repair of the tissues.

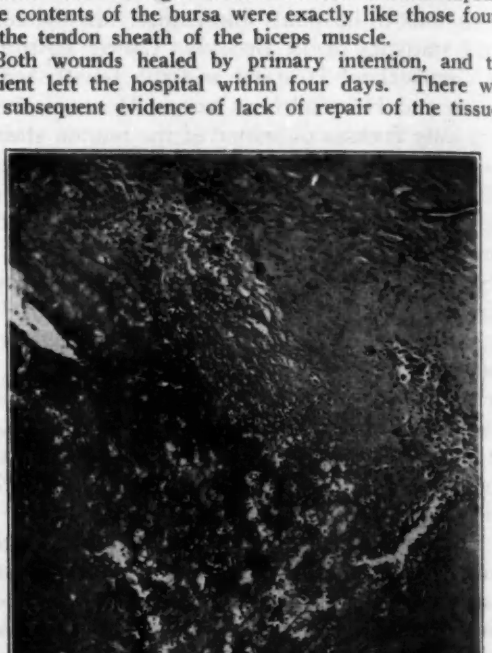

Fig. 4.—Low power magnification of a section showing an area of necrosis and granulation tissue surrounded by giant cells.

Pathologic Report.—The first intimation about the true nature of the tumor mass came from Dr. I. Davidsohn, the hospital pathologist, who recognized in the histologic picture a syphilitic pattern.

The tumor was sausage shaped (6 by 2 cm.). It consisted of a thin capsule (1 mm.) with a red, smooth, glistening outer surface, with deposits of a soft yellow material on the inner surface. About 2 cm. above the proximal end of the tumor, an almond-shaped mass was found attached to the inner surface of the sheath of the long head of the biceps muscle. It measured 24 by 19 by 4 mm. It was pink, with yellow areas and strands of loose connective tissue attached to it. The sectioned surface was gray. Several pieces of membranous red tissue measured about 8 by 5 by 2 mm.

Microscopic Report.—A thick layer of granulation tissue was found. Large masses of lymphocytes mixed richly with plasma cells were present in accumulations as well as diffusely. The largest accumulations were at the periphery of the capsule just below the fat tissue. The relation of these massive accumulations to blood vessels was intimate and striking, not unlike the picture seen in the adventitia of the aorta in cases of syphilitic aortitis. There was lymphocytic and leukocytic infiltration in the wall. Amorphous material in the innermost layer of the wall showed the type of necrosis seen in the contents of gummatous lesions. Sections from the node attached to the sheath of the tendon of the biceps muscle showed in some places, at the periphery, similar thick collagenous fibers infiltrated with lymphocytes and plasma cells.

Frozen sections from the amorphous contents of the bursa revealed droplets of sudanophilic material.

The changes were compatible with a syphilitic granuloma.

Fig. 5.—Higher magnification of the section presented in figure 4, showing many giant cells at the border of the necrotic area.

Olecranon Bursa: Pathologic Report.—The specimen labeled bursa of the olecranon was a sac, irregularly shaped, measuring 55 by 50 by 8 mm., with club-shaped projections extending into the bursal cavity. When the cavity was opened it was seen to be filled with a yellowish, soft, amorphous tissue, similar to the material which was present in the specimen from the arm. A surface sectioned through the club-shaped projections showed similar contents in the center of the cavity, with a translucent white tissue in the walls surrounding it.

Microscopic Report.—Sections showed areas of necrosis surrounded by granulation tissue in the midst of thick layers of dense fibrous tissue. The necrotic material in the center of the nodes was eosinophilic. It was amorphous and caseous, with an admixture of some of the cells from the granulation tissue, which formed a wall around it. Among the fibroblasts, there were present relatively large numbers of giant cells with peripherally located nuclei, which were oval and vesicular, with their long axes arranged parallel and radially. The giant cells resembled those seen in tuberculosis and in gummas. The picture was characteristically that of a syphilitic gumma.

SYPHILITIC BURSITIS

This entity was first mentioned by Verneuil,[19] in 1866 and 1877. In 1876, the elder Keyes [20] collected 14 cases from the general literature and analyzed 27 cases. He published an article: "Syphilis as Affecting Bursae." Keyes, Jr., reported 5 cases, 2 of which were included in the elder Keyes' article. The classic article of Churchman [21] awakened interest in this condition, and he coined the term "luetic bursopathy of Verneuil", in recognition of Verneuil's early description and the emphasis placed on syphilis of bursas. Codman stated: "I have never recog-

Fig. 6.—Two spirochetes are shown in an area of necrosis.

nized a case of syphilitic bursitis in the shoulder but I have seen 2 cases of syphilitic ulcer, which presumably involved the subcutaneous bursae."

The British literature is totally silent on syphilitic bursitis. This silence is strange, since syphilitic diseases of joints have been well studied by the British. Symmetric synovitis of the knee in congenital syphilis has been known in England as Clutton's disease. Syphilitic involvement of joints was mentioned in England as early as 1498 by Peter Martyr, but was actually described by Ricket in 1853.

The interval between the primary lesion and the development of syphilitic bursitis varies from a few months to ten years. According to Churchman's tabulation, in 9 cases syphilitic bursitis

20. Keyes, E. L., Sr.: Am. J. M. Sc. **71**:349, 1876.

21. Churchman, J. W.: Am. J. M. Sc. **138**:371, 1909.

occurred in the secondary stage of syphilis and in 17 in the tertiary stage.

Patients with syphilitic bursitis have either no pain or only very slight pain. Indolent bursitis without a history of trauma should be suspected as being due to syphilis. Occasionally housemaid's knee has proved to be syphilitic. Indolent bursitis about the knee or the elbow in children with Hutchinson's triad should be suspected as being syphilitic. Roentgenograms are of no value, since the process does not involve the adjacent bone.

In the differential diagnosis between syphilitic bursitis and other entities, tuberculosis has been considered. However, according to Barnard,[22] tuberculosis attacks persons in the extreme age groups, whereas syphilis attacks, as a rule, middle-aged persons.

The bursas most commonly involved are the prepatellar, the subpatellar and those about the elbow.

Pathologically, a syphilitic bursa shows hyperplasia of connective tissue with subsequent degeneration of its contents: yellowish, viscid, coagulable fluid (Garner and Schoch[23]). If syphilitic bursas break down, deep ulcers or projecting fungating granulation masses form.

22. Barnard, H. L.: Clin. J. **23**:188, 1904.
23. Garner, V. C., and Schoch, A. G.: Syphilitic Bursopathy of Verneuil, Arch. Dermat. & Syph. **24**:591 (Oct.) 1931.

Treatment consists in most cases in surgical removal, as the surgeon rarely suspects the real nature of the disease. The older syphilologists obtained many cures by using merely mercury and iodides. According to Churchman, this type of mixed treatment brought satisfactory results in about forty-six days.

CONCLUSIONS

Syphilis of tendons and bursas should be suspected more often in the diagnosis of tendinitis and bursitis.

The reasons for the scarcity of reports in modern literature as contrasted with the older literature are: (*a*) the adequate and more universal treatment of syphilis with arsenicals and bismuth, which either modify or obviate the pathologic changes of syphilis, and (*b*) the intense diagnostic acumen of the older syphilologists in the absence of serologic tests.

In the case of syphilis of the tendon of the long head of the biceps muscle and of the olecranon bursa herewith presented, for the first time, the diagnosis of syphilis of these structures has been, I believe, definitely proved by the presence of Treponema pallida in the granulation tissue.

The tendon of the long head of the biceps muscle is more vulnerable than other tendons to both specific and nonspecific infections.

TUBERCULOUS ABSCESS OF THE THYROID GLAND

REPORT OF A CASE AND REVIEW OF THE LITERATURE

CAPTAIN R. W. POSTLETHWAIT AND CAPTAIN PHILIP BERG JR.
MEDICAL CORPS, ARMY OF THE UNITED STATES

Formation of an abscess in the thyroid gland is an infrequent manifestation of tuberculosis. Rankin and Graham stated that "such progression of the disease (into cold abscess) is extremely rare." In a review of the literature we have been able to find only 26 cases. No reported case is similar to the one detailed in our paper in that a tuberculous abscess of the thyroid developed in this patient during the secondary stage of syphilis.

Coller and Huggins stated that two types of tuberculosis of the thyroid gland are seen: miliary and caseating. The miliary type is found with a generalized tuberculous infection. In the caseating type the gland may necrose and soften to form masses of tuberculous caseating material or may liquefy to form a cold abscess. Lindsay and Mead reviewed the literature in 1934 and found recorded about 255 cases of tuberculosis of the thyroid. Of these tuberculous conditions, 125 were discovered at operation or on histologic study of the gland following operation. The remaining 130 were found at autopsy and consisted chiefly of miliary tubercles of the thyroid associated with acute generalized miliary tuberculosis. In 1933, Van Ravenswaay and Van Ravenswaay collected 107 cases in which tuberculosis of the thyroid was discovered at operation. During our search for reports of tuberculous abscess of the thyroid, we found 21 additional cases of tuberculosis of the thyroid reported since 1933, in 4 of which abscesses occurred (Tinker; Dean and Hall; Dinsmore; Ruthe; Louria and Louria; Keynes; Uraz; McGregor and Peacock; Phillips and Waldron; Baz and Perrin; Hare and Simpson; Comando). These do not include reports of the miliary type, which appears to be of less clinical interest.

To the two types discussed by Coller and Huggins might be added the sclerosing form, as reported by Budd and Williams, by Higgins and by others. In this type the thyroid glands are small, fixed and hard and are thought to represent arrested or healed tuberculosis. Budd and Williams, however, stated that "sclerosing tuberculosis of the thyroid results from circulating toxins." Jaffé reported 4 cases in which the histologic changes "are identical with those described as a benign, sclerosing form of tuberculosis of the thyroid." He stated the belief that these conditions are the result of focal involutional changes and are nontuberculous. Therefore, some doubt now exists as to the actual cause of the sclerosing type.

Excellent reviews of tuberculosis of the thyroid were published by Coller and Huggins in 1926, Rankin and Graham in 1932, Van Ravenswaay and Van Ravenswaay in 1933 and Lindsay and Mead in 1934. However, no paper has been devoted to tuberculous abscess alone, and no review has contained all the recorded cases of tuberculous abscess of the thyroid. For this reason, the reported cases are abstracted briefly.

CASE 1 (Schwartz).—The patient was a 30 year old man who complained of swelling in the neck, dysphagia and dyspnea of several weeks' duration. Examination showed swelling of the right lobe of the thyroid, with deviation of the trachea to the left. The right pupil was smaller than the left, and there was paralysis of the right vocal cord. No tuberculosis was found elsewhere. Incision and drainage of the cold abscess of the right lobe yielded 60 to 70 cc. of thick, yellow, granular pus. The patient recovered. In a guinea pig inoculated with the pus tuberculous lesions were produced.

CASE 2 (Rolleston).—The patient was a 23 year old woman who had paraplegia, associated with tuberculosis of the first lumbar vertebra and of the upper part of the sacrum. There was also pulmonary tuberculosis. During life there were no symptoms referable to the thyroid gland. At autopsy there was found an abscess of the left lobe of the thyroid with two openings into the esophagus. The lymph nodes of the neck were also involved.

CASE 3 (Fraenkel).—The patient was a 55 year old woman who had had swelling of the neck for four months. Hoarseness, dyspnea and dysphagia were present. A diagnosis of malignant tumor was made. An attempted extirpation of the thyroid was extremely difficult, and the patient died shortly afterward of purulent mediastinitis. Autopsy showed a tuberculous abscess of the right lobe of the thyroid gland and also pulmonary tuberculosis.

CASE 4 (Berard).—The patient was a 23 year old man whose thyroid became enlarged. There was no pain, and no signs of compression were present. The diagnosis was cystic adenoma. An operation showed a

cold abscess of the thyroid. He was cured after the operation but died some time later from osseous tuberculosis and septicemia.

CASE 5 (Roger and Garnier).—The patient was a 34 year old woman who had pulmonary tuberculosis and tuberculous pharyngitis. She was admitted to the hospital during the last trimester of pregnancy and died seventeen days after delivery. During life there were no symptoms referable to the thyroid itself. At autopsy there was a cavity in the pyramidal lobe, which contained thick pus. Tubercle bacilli were found in this material.

CASE 6 (Clairmont).—The patient was a 2 year old boy who had previously been well. Seventeen days before his admission to the hospital the mother noted slight swelling of the thyroid, and ten days before admission the swelling increased and was accompanied by restlessness and slight fever. Examination on admission showed a swelling, the size of a walnut, in the midline in the region of the thyroid gland. This was firm, smooth and tender; it was displaceable in either direction, but more so horizontally, and it moved with swallowing. At operation an abscess containing thick gray fluid was found. The cavity was curetted and packed. Two fistulas followed which required excision, but the patient eventually recovered. Histologic examination showed tuberculosis.

CASE 7 (Pupovac).—The patient was a 42 year old man who had noted a walnut-sized, painless swelling in the middle of the neck after coughing seven months previously. Gradual enlargement occurred. Examination showed a swelling the size of a goose egg, which was soft, smooth and fluctuant. There were also signs suggesting tuberculosis in the apex of the left lung. A diagnosis of cold abscess was made, and aspiration yielded thin pus. At operation the wall of the abscess and the remainder of the isthmus were excised with radical excision of the lymph nodes of the neck. The wound healed well, and histologic examination showed tuberculous granulation and tubercles in the wall of the abscess.

CASE 8 (Corner).—The patient was a 9 year old girl who had had swelling of the neck for one year. Examination showed the right lobe of the thyroid to be enlarged. The lower pole was soft and fluctuant. There was a sinus at the apex of the left lobe. At operation an abscess of the right lobe was opened and "one to two drachms of pus" evacuated. Sections of the wall of the abscess showed chronically inflamed thyroid tissue and tubercles. No tuberculosis was found in the lungs prior to operation. The patient died seven months later from tuberculous meningitis and acute generalized tuberculosis, the wound having failed to heal.

CASE 9 (Lediard).—The patient was a 21 year old man. The signs and symptoms were not stated. No tuberculosis, however, was found elsewhere in the body. At operation an ounce or more of seropurulent material was removed from the left lobe of the thyroid gland. Recovery was prompt. No tubercle bacilli were found in the pus, and cultures were negative. Histologic examination of excised tissue showed tubercles.

CASE 10 (von Schiller).—The patient was a 17 year old youth who had chronic pulmonary tuberculosis. He first noted a tumor the size of a nut in the left lobe of the thyroid. This gradually increased over a period of several months to the size of a fist. Dyspnea was present. The enlargement was soft. At operation a cold abscess, containing 90 cc. of pus, was evacuated. Tubercle bacilli were found in the pus. The patient recovered.

CASE 11 (Lenormant).—The patient was a 40 year old man who had a cold abscess of the isthmus of the thyroid, the size of a black walnut. He also had a cold abscess over the right greater trochanter. Incision and drainage of the abscess of the thyroid were carried out. A fistula formed which persisted for about two and one-half months. No laboratory confirmation of the cause of the abscess was given.

CASE 12 (Halstead).—The patient was a 28 year old woman who had had a swelling in the neck for one year. It gradually enlarged to the size of a small orange, and a month before operation it caused pain, dyspnea and dysphagia. Poultices were applied, and after a few days an opening formed, discharging thick pus. This was followed by discharge of large quantities of pus and caseating material at intervals of a few days, without a decrease in the size of the mass. At operation an abscess cavity of the left lobe of the thyroid gland was found, extending down behind the sternum. Prolonged drainage occurred but was followed by recovery. No organisms were found, but histologically tuberculosis was present.

CASE 13 (Pollag).—The patient was a woman of 59 years. There was a family history of tuberculosis, and her past history suggested pulmonary tuberculosis. She had had a goiter from childhood. Three years before she began having difficulty with the right knee. She was admitted to the hospital, and femoral amputation was carried out for tuberculosis of the right knee joint. Examination at this time showed an infection in the apex of the left lung. There was a moderate enlargement of the thyroid, with a walnut-sized node in each lobe. Nineteen days after amputation of the leg the skin over the thyroid gland became red, warm and tender. Seven days later fluctuation appeared. At operation thin fluid pus was obtained and an abscess of the isthmus drained. The patient eventually recovered. Tubercle bacilli were present in the pus, and the wall of the abscess contained tubercles histologically.

CASE 14 (Pollag).—The patient was a 74 year old woman whose neck had always been large. Five days before admission there was increased swelling and then a rapid increase in size, after which she came to the clinic. A diagnosis of "cystic struma with intracystic blood" was made. Examination showed the right lobe to be moderately enlarged and firm. In an area nearer the midline on the right there was another soft fluctuant swelling. The skin was red in the center, bluish red in the surrounding area and entirely blue around the periphery. No tenderness was present. Aspiration was followed by incision and drainage, from which a creamy exudate from gray-green to brownish in color was

obtained. The patient recovered. The aspirated pus contained tubercle bacilli.

CASE 15 (Labey).—The patient was a 76 year old woman who had a large goiter with symptoms of suffocation. The left lobe of the thyroid was involved, extending behind the sternum and pushing the trachea and the larynx to the right. Fluctuation was present. Incision was made, and caseous pus was found filling a cavity in the left lobe. The cavity extended into the upper mediastinum. The left lobe and the isthmus were removed, the mediastinal tract curetted and several hard masses in the right lobe removed. Histologic examination showed tuberculosis.

CASE 16 (Jean).—The patient was a 42 year old man who complained of swelling in the neck, with hoarseness and dysphagia of several months' duration. A little to the right of the midline there was a round tumor, which felt cystic and was tender. At operation pus was obtained, the right lobe removed and the wound closed without drainage. This remained healed for seven months. Tubercle bacilli were found in the pus. The abscess was thought to be secondary to pulmonary tuberculosis.

CASE 17 (Vallata).—The patient was a 62 year old woman who had had a goiter for sixteen years. Several weeks prior to her admission to the hospital pain developed. This was relieved by hot packs but later returned and was accompanied by dysphagia and dyspnea. Occipital headache was also present. When she entered the hospital her general condition was poor. There was slight fever. The thyroid was diffusely enlarged, the left lobe more so than the right. The left lobe was firm and tender. Hot packs were applied for seven days, after which distinct fluctuation appeared. Incision and drainage were done, and an odorless seropurulent liquid was obtained. The patient recovered. No organisms were found. Histologic examination showed tuberculosis.

CASE 18 (Jones).—The patient was a 64 year old man with a history of rapid increase of swelling in the neck over a period of three months. Dysphagia and hoarseness were present. Examination showed a tumor over the isthmus. This moved on deglutition and was tense, encapsulated, nonfluctuant and not painful; the skin was not adherent. The whole tumor was freely movable up and down but not laterally. At operation the capsule was broken during dissection, and there escaped a thick, creamy, yellow pus, containing small caseous particles. The wound healed with ultraviolet therapy. No tubercle bacilli were found, but a guinea pig inoculated with the pus died of generalized tuberculosis.

CASE 19 (Dimtza).—The patient was a 69 year old woman who had had a goiter for thirty years. Striking growth, with pressure on the surrounding structures, had occurred in the two to three months prior to admission. Loss of weight had occurred. The swelling was principally on the left side. Aspiration produced a purulent, grayish brown liquid. Under intensive roentgen therapy a large opening formed at the site of a puncture made with a needle. This gradually healed over a period of eighteen months. Tubercle bacilli were obtained on culture of the pus, and tuberculosis developed in a guinea pig inoculated with the pus.

CASE 20 (Starlinger).—The patient was a 2 year old boy. For fourteen days there had been swelling of the neck, with some respiratory difficulty. Examination showed a walnut-sized mass on the right side. This was smooth and not tender and moved with swallowing. Slight stridor was present. At operation greenish yellow fluid was found. The cavity was packed. A fistula formed and was later excised, and healing finally occurred. One year later the patient was seen and appeared slightly myxedematous. Cultures of the pus were negative, but histologic examination of the tissue showed tuberculosis.

CASE 21 (Starlinger).—The patient was a 64 year old man who had had severe dyspnea and increase in the size of the neck for one year. For six months there had been rapid growth of the goiter, dysphagia and pain radiating to the back of the head. He also noted decreased hearing. Examination showed a tumor the size of a fist on the left side. This was firm, smooth, tender and elevated on swallowing. There was paralysis of the left recurrent nerve, and the trachea deviated to the right. At operation excision of the tumor, which extended behind the esophagus, was attempted, but the abscess was opened and an esophageal fistula was found. Therefore, extirpation of the left lobe of the thyroid was carried out, and gastrostomy had to be done. The patient died four months later of erosion of a large vessel. At autopsy there were found old tuberculous peritonitis, pulmonary tuberculosis and tuberculosis of the thyroid gland.

CASE 22 (Starlinger).—The patient was a 48 year old man who had had a goiter for thirty years. Three weeks before admission to the hospital he had noted pain in the neck, especially with cough. After fifteen days the swelling became firm. The patient lost about 22 pounds (10 Kg.) during the acute phase of the illness. Examination showed on the right side of the neck a tumor the size of a fist, which was firm and irregular and moved with swallowing. The lower pole was tender. At operation the abscess was accidentally opened, and copious pus appeared. The right lobe of the thyroid was removed, and the resulting wound was packed and eventually healed. Recovery occurred. Histologic examination showed tuberculosis.

CASE 23 (Uraz).—The patient was a 33 year old woman who had first noted swelling of the neck five years prior to admission to the hospital. The tumor gradually increased to the size of an orange. There was no pain. Exertional dyspnea was present. Examination showed a round regular tumor in the median line of the neck. The tumor was painless, hard, smooth and transversely mobile and moved with swallowing. At operation greenish pus escaped when the tumor was seized with a forceps. It was then incised and 80 cc. of pus obtained. No tubercle bacilli were found on direct examination, culture or inoculation of a guinea pig, but the wall of the abscess showed tuberculosis histologically. The patient recovered.

CASE 24 (Keynes).—The patient was a 26 year old man who was under treatment for pulmonary tuberculosis. About six months before operation the patient had noted nervousness, loss of weight and tremors; exophthalmos developed. There was a painful lump on the right side of the neck. Examination showed a hard nodule in the right lobe of the thyroid. At operation the right lobe was removed, and some caseous pus escaped during the process. The wound healed uneventfully, and the patient recovered. A culture of the pus yielded a profuse growth of the tubercle bacillus, and histologic examination showed tuberculosis.

CASE 25 (Hare and Simpson).—The patient was a 65 year old woman who was admitted because of swelling of the left lobe of the thyroid of unknown duration. Examination showed the left lobe of the thyroid to be enlarged and firm and compressing the trachea. At operation an opening was made into the tumor, and a large amount of greenish and caseous material escaped. The abscess cavity had destroyed most of the left lobe of the thyroid and had dissected through most of the supraclavicular space. The wound was drained and healed with roentgen therapy. The patient recovered. Cultures were negative, but tuberculosis was found on histologic examination.

CASE 26 (Hare and Simpson).—The patient was a 30 year old woman who was admitted to the hospital because of a lump in the neck of three weeks' duration. There had been increase in the size of the tumor but no toxic or obstructive symptoms. Examination showed a small mass in the region of the isthmus of the thyroid. At operation an abscess cavity, extending behind the manubrium, was found filled with fairly thick, greenish yellow pus. The wound was closed with drainage. Roentgen therapy was given. There were two recurrences during the next two years. The patient was followed for a total of six years and remained well. Cultures of the pus showed Staphylococcus aureus, but smears revealed no organisms. Tissue removed showed tuberculosis histologically.

INCIDENCE

As stated previously, tuberculous abscess of the thyroid gland is rare. In the cases studied (the 26 from the literature and our own) there were 14 male patients and 13 female. Their ages varied from 2 to 76 years, the average age being 39.2 years.

SYMPTOMS

In 2 cases in which the abscess was found at autopsy, there were no symptoms referable to the thyroid gland during life. In all the other cases the patients complained of swelling in the neck, this usually being the principal complaint. Only 5 patients gave a definite history of enlargement of the thyroid prior to onset of the symptoms of abscess. The duration of symptoms varied from a few days to six months, in the majority of cases being two months or less. Pain alone was not a prominent complaint, although dysphagia of varying degree was mentioned in 8 case reports. In about one third of the cases dyspnea was present, usually not severe. Hoarseness and dysphonia were mentioned only occasionally. Loss of weight was not frequent. In only 1 case were there symptoms and signs of hyperthyroidism.

SIGNS

A mass in the region of the thyroid gland was the most consistent finding. The abscess was on the right side in 10 cases, on the left side in 9 and in the median portion in 7 (location not stated in 1 case). The size of the swelling varied from that of a "walnut" to that of a "large fist." The mass was usually described as smooth; most often as firm, although fluctuation was present in about one third of the cases. Tenderness was mentioned also in about one third of the case reports. Lateral mobility and upward movement of the mass on deglutition were frequently described. Fixation was not common. Increased local heat and redness of the skin were mentioned only occasionally, and adherence of the mass to the skin was rarely seen. In 2 cases discharging sinuses were found; in 2 there was unilateral paralysis of the vocal cords, and in 1 the homolateral pupil was small.

Tuberculosis was found elsewhere in the body in 9 cases, in 7 instances in the lungs. It should be stated that a number of the reports deal briefly with signs and symptoms, so that this summary is incomplete, although presenting a reasonably accurate clinical picture.

DIFFERENTIAL DIAGNOSIS

Acute suppurative thyroiditis (Weinstein; Cochrane and Nowak; Greenfield and Curtis) nearly always follows an acute infection elsewhere in the body. There is a rapid, painful swelling of the gland, or more often of one portion of the gland. Chills, fever, general malaise and anorexia occur. Dysphonia, dysphagia and other symptoms due to pressure may be present. The patient appears ill and is unable to extend the neck or tilt the head away from the side of the lesion. The skin over the swelling is usually red, with increased local heat. The abscess is smooth and tender and may move with swallowing. Fluctuation may or may not be elicited. There are fever and leukocytosis.

Acute nonsuppurative thyroiditis is similar in most respects to the suppurative form. Fluctuation is absent, and the lesion usually responds promptly to treatment, or suppuration occurs.

With hemorrhage into a cystic adenoma, there is a history of a preexisting enlargement or nodule in the thyroid, with a sudden increase in size, frequently accompanied by pressure symptoms. The enlargement may feel soft and cystic or be very tense from the contained blood. Discoloration of the skin may be present. Signs of infection are lacking.

A malignant neoplasm (Pemberton and Haines) in the thyroid gland in most cases develops on the basis of a preexisting benign goiter. Rapid growth of a long-standing adenoma or sudden development of a mass in a previously normal gland may occur. Pain and pressure symptoms may be early and severe. The mass is very firm and irregular, with fixation to the surrounding structures.

Struma lymphomatosa (Moore and Lloyd; McSwain and Moore) nearly always occurs in women, most frequently in the first decade. The enlargement is present for an average of five years and grows slowly. There is loss of weight only occasionally. The enlargement is usually uniform, firm and slightly irregular. Fixation is rarely present.

Riedel's struma (Goodman) is more common in women (3 to 1), 60 per cent occurring between the fourth and fifth decades. The usual duration is about ten months. Thirty per cent have a history of preexisting goiter. Loss of weight is common, as are nervousness and palpitation. Pain and pressure symptoms are frequent and may be severe. Only one lobe is involved in about half of the cases. The growth is stony hard, and fixation to surrounding tissue is usually present.

Actinomycosis is rare. There is marked induration of the area at first, after which softening takes place. Sinuses form, and the discharge contains the characteristic granules.

Gumma (Stokes) of the thyroid is a comparative rarity. It seldom causes symptoms other than those of pressure on the trachea and of myxedema, which occurs only occasionally. There is hardness or woody infiltration of the gland. Adherence to or ulceration into surrounding skin occurs in a number of cases. Any portion or all of the gland may be involved. Positive serologic reactions and other signs of syphilis will aid in differentiation. Response to treatment is excellent in reasonably early stages of the disease.

Opinions as to the expected ability of the clinician to diagnose this lesion vary greatly. Cohen stated the belief that a diagnosis should be made preoperatively in most cases of tuberculosis of the thyroid, while Hare and Simpson stated that the clinical diagnosis is practically impossible. The truth, particularly as concerns cold abscess, probably lies halfway between these two views. Because of the rarity of the lesion it is seldom considered as a possibility.

TREATMENT

Surgical drainage of the abscess is indicated. Simple incision with packing of the abscess cavity is adequate, although in several reported cases excision of the involved tissue has been done with good results. In 1 case ultraviolet therapy was used, and in 3 cases roentgen therapy was given. The precise value of these two factors was not definitely established.

PROGNOSIS

In 2 of the reported cases the abscess of the thyroid was found at autopsy. In both instances there was tuberculosis elsewhere in the body, and the abscess was probably not the direct cause of death. Three patients died postoperatively. One patient died of purulent mediastinitis following attempted excision of the portion of the thyroid containing an abscess. The second patient died of miliary tuberculosis seven months after incision and drainage of the abscess. The third patient died four months after operation of hemorrhage from erosion of a large vessel.

Fig. 1.—Photograph of the patient before operation, showing enlargement of the right lobe of the thyroid.

The remaining patients recovered, although in several there was chronic drainage or recurrence of the abscess. In only 1 instance was the abscess followed by a slight myxedema. Generally speaking, therefore, the prognosis is good with complete recovery.

REPORT OF CASE

A 24 year old Negro private was admitted to the hospital on May 15, 1943, because of a sore throat of

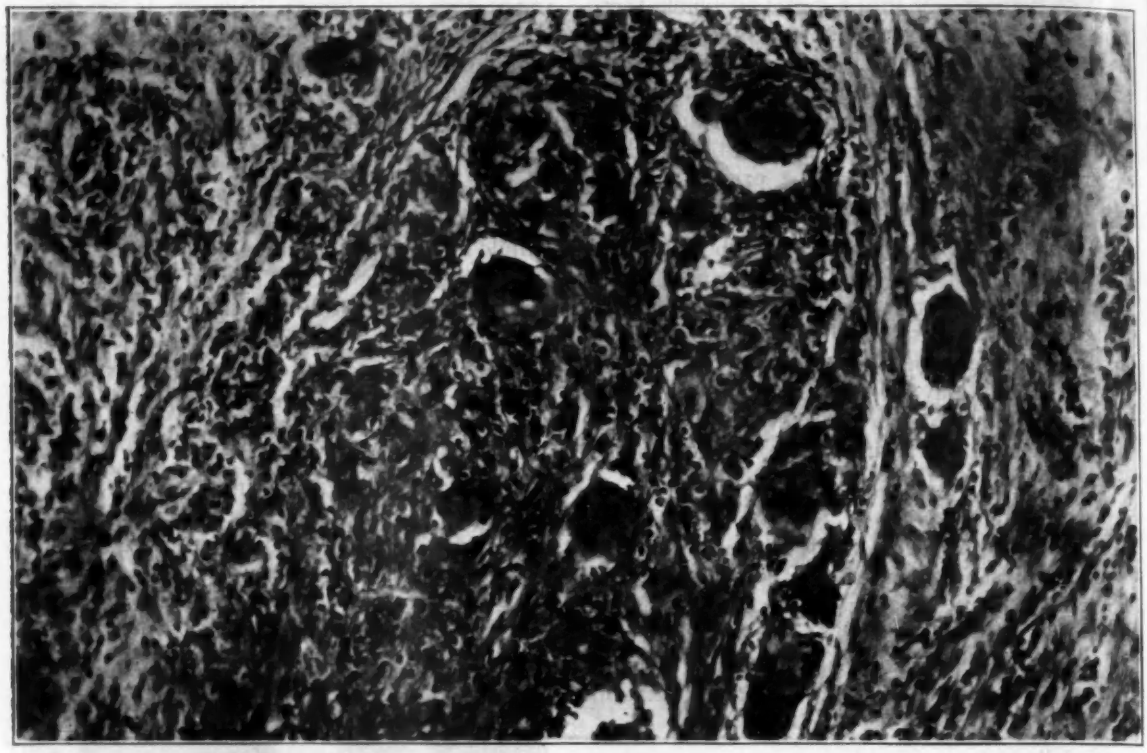

Fig. 2.—Photomicrograph of the tuberculous granuloma in tissue removed at the second operation. (United States Army Medical Museum specimen 77603.)

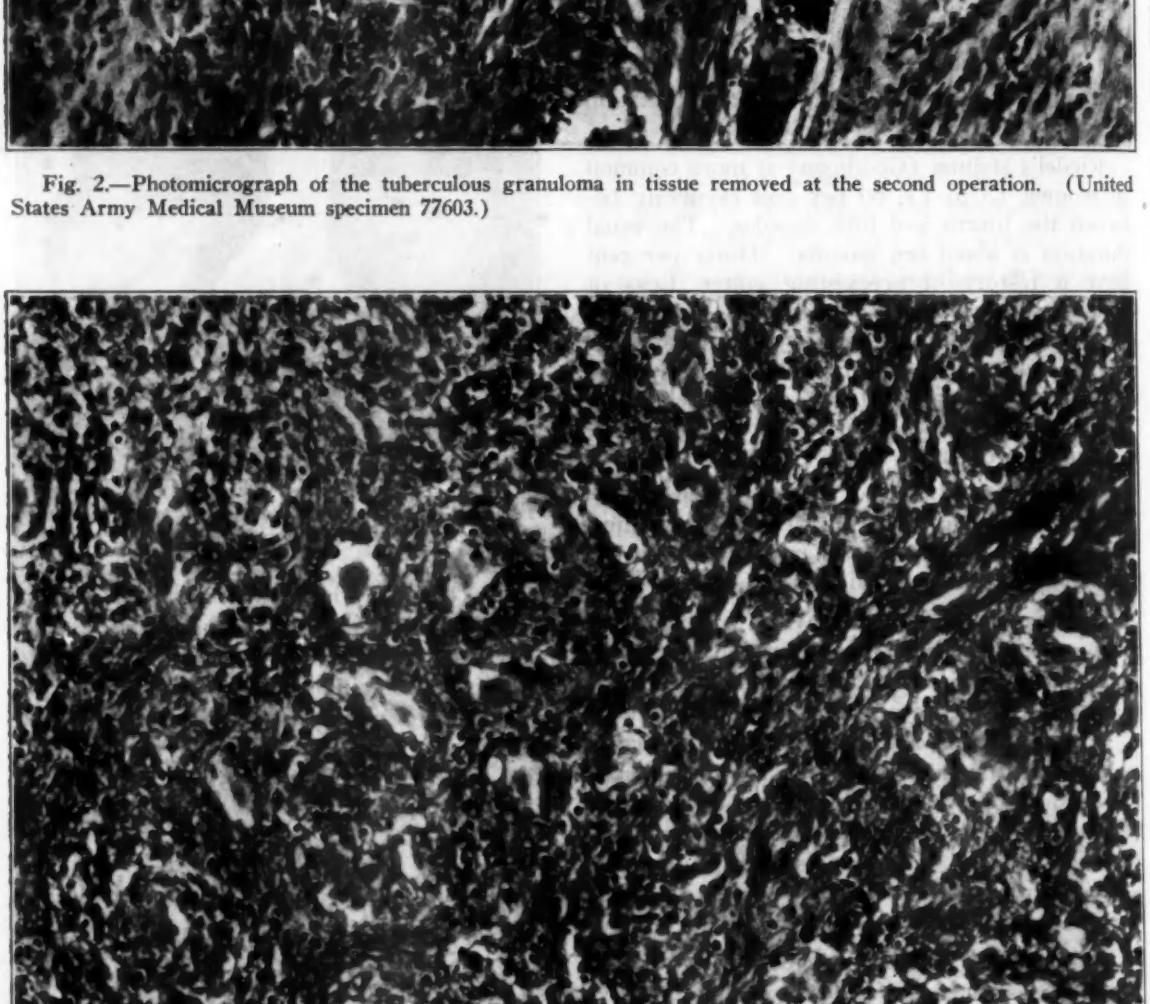

Fig. 3.—Photomicrograph of remnants of thyroid follicles in tissue removed at the second operation. (United States Army Medical Museum specimen 77602.)

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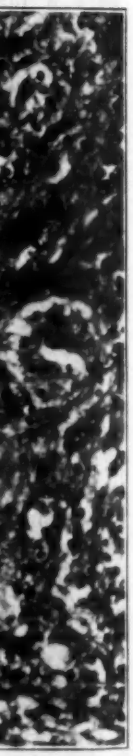

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three weeks' duration. The soreness had not been severe at any time, but dysphagia had been persistent. During this time he had also noted enlarged nodes in the back of the neck and the gradual appearance of a mass in the region of the thyroid gland. Five days before his admission an ulcer had developed on the penis. His last sexual intercourse had been with a prostitute one month previously. The past history was irrelevant. There had been no previous enlargement of the thyroid.

On examination the patient did not appear acutely ill. There was no fever or tachycardia. The tonsils were enlarged, injected and superficially ulcerated. A firm, smooth, slightly tender mass, about the size of a small lemon, was present in the region of the right lobe of the thyroid. This moved with swallowing and was not attached to the skin. The lymph nodes in the posterior cervical region were enlarged but not tender. In the right parafrenal area of the penis a small, superficial, sharply circumscribed, painless ulcer was seen.

Accessory clinical data showed a red blood cell count of 4,400,000, a hemoglobin content of 90 per cent and a white cell count of 6,700, with 75 per cent polymorphonuclear forms. Urinalysis gave normal results. Material from the penile ulcer showed Treponema pallidum on dark field examination. Kahn reactions were repeatedly positive. A Frei test gave a negative reaction and a roentgenogram of the chest showed nothing abnormal.

The day following the patient's admission, macular lesions were noted over the antecubital regions, the back and the legs. Antisyphilitic therapy was given, the patient receiving an arsenical (mapharsen) intravenously twice weekly and bismuth subsalicylate intramuscularly once a week. With this treatment the tonsillitis rapidly subsided, the ulcer on the penis healed and the enlarged lymph nodes became smaller. The right lobe of the thyroid, however, became a little larger and remained firm and only slightly tender. The skin overlying the right lobe was somewhat reddened. No fixation of the mass was present. There were little pain, no dysphagia and no limitation of extension of the neck. No systemic changes were present except an elevation of temperature from 99.0 to 99.8 F. in the afternoons. The basal metabolic rate was +4. Approximately three weeks after the patient entered the hospital fluctuation in the mass was elicited.

Aspiration of the right lobe of the thyroid yielded purulent material. The abscess was then incised under local anesthesia, and about 75 cc. of thick, yellowish gray purulent material was obtained. The abscess cavity outlined accurately the entire right lobe of the thyroid. An attempt was made to encourage healing by granulation from the bottom of the wound by packing the abscess cavity with petrolatum gauze. Despite this a sinus formed and was excised ten weeks after the original incision. Another sinus formed, and final healing did not take place until four weeks later. The wound has remained healed since the patient's discharge from the hospital, four months prior to the time of writing. He feels well and is able to carry on his full duties as a soldier. There is nothing to suggest myxedema and no evidence of tuberculosis elsewhere in the body.

Unfortunately the material obtained at operation was not stained for acid-fast bacilli nor inoculated into a guinea pig. Dark field examination revealed no spirochetes. Routine cultures of the pus were sterile. Later cultures of the discharge during healing all showed Staphylococcus aureus. A small mass of necrotic material removed at the first operation showed no cellular detail on histologic study, so that no diagnosis could be made. When the sinus tract was removed the excised tissue showed tubercles and a few structures suggesting thyroid follicles. Special stains of this tissue showed acid-fast bacilli.

COMMENT

Louria and Louria stated: "For undoubted proof of the existence of tuberculosis of the thyroid gland, one would expect characteristic histological evidence, substantiated by the demonstration of tubercle bacilli on culture of the tissue or through guinea-pig inoculation." However, Hedinger, Lediard, Corner, Halstead, Mosiman, Plummer and Broders and most subsequent investigators have accepted the histologic evidence as adequate for a diagnosis of tuberculosis.

In the case presented some doubt may be justifiably expressed of the diagnosis of tuberculosis in the presence of secondary syphilis. Van Ravenswaay and Van Ravenswaay stated: "It is probable that in lesions of clinical importance, after lues has been excluded, a diagnosis of tuberculosis can be made from the microscopic picture with a high degree of accuracy." On a histologic basis alone, therefore, we would be unable to differentiate absolutely between syphilis and tuberculosis. Tubercle bacilli, however, were demonstrated in the excised tissue, and on this basis there would seem to remain little doubt as to the cause of the lesion. It may be mentioned that we were unable to find a reported case in which acute suppurative thyroiditis developed during primary or secondary syphilis.

It is possible, however, that during the acute phase of syphilis a locus minoris resistentiae was created in the thyroid by the syphilis, thereby lowering resistance to such a point that the tubercle bacilli were able to initiate a pathologic process. Our inability to demonstrate tuberculosis elsewhere in the body does not detract from the exactness of the diagnosis. Rankin and Graham found no tuberculosis elsewhere in their 21 cases, and no mention of tuberculosis elsewhere in reports of 91 of 97 cases in which adequate information was available. In only 9 of the 26 reported cases of tuberculous abscess of the thyroid were tuberculous lesions found elsewhere in the body.

SUMMARY

Tuberculous abscess of the thyroid gland may appear at practically any age, and the occurrence is about equally divided between the sexes. In only 5 of the 27 cases was there a definite history of a preexisting goiter. The average duration of symptoms was about two months. The symptoms are swelling in the region of the thyroid, with pressure symptoms, such as dysphonia, dysphagia and dyspnea, of variable severity. Pain is not prominent. The mass is usually firm and smooth, occasionally tender and fluctuant in about one third of the cases. Fixation is not common. After surgical drainage the prognosis is good. The diagnosis is usually made on the basis of histologic study of the excised tissue and is infrequently made prior to operation.

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ROLE OF ALLERGY IN DELAYED HEALING AND IN DISRUPTION OF WOUNDS

I. ANTIGENICITY OF CATGUT

HOWARD C. HOPPS, M.D.

CHICAGO

The general incidence of disruption of wounds has been estimated to be from 1.5 to 2 per cent following abdominal operations.[1] Over 1,400 cases of such disruption have been recorded.[2] Since approximately 35 per cent of patients suffering such disruption of wounds die,[3] it can be seen that this complication presents a major surgical problem and accounts for a considerable number of postoperative deaths. The increased morbidity which attends breakdown or delayed healing of wounds is obvious. Not only is the time of hospitalization and of recovery greatly prolonged, but the incidence of postoperative hernia is greatly increased.

In order to understand the mechanism of dehiscence of wounds it is necessary to understand the processes which normally occur to bring about the healing of surgical wounds. The reader is referred to the excellent review article of Arey [4] and to the papers of Carrel,[5] Harvey,[6] Loeb [7] and others [8] for a discussion of these fundamental processes.

Of the predisposing or causative factors which lead to breakdown of wounds, it may be said that age and sex are probably not significant, since these vary widely, depending on the series of cases studied.[9] Similarly, the site of abdominal incision does not appear to be an important factor. Much has been written about the technic of closure of wounds with respect to decreasing the incidence of disruption, and some surgeons have reported that as the result of using certain prescribed technics the incidence of breakdown of wounds in their patients is almost nil.[10] Yet these same technics fail in the hands of other, equally skilled, operators. Suture material too has come under scrutiny as a possible factor leading to evulsion of wounds.[11] It is common

From the Department of Pathology, University of Chicago.

1. (*a*) Hartzell, J. B., and Winfield, J. M.: Disruption of Abdominal Wounds, Internat. Abstr. Surg. **68**:585, 1939; in Surg., Gynec. & Obst., June 1939. (*b*) Hinton, J. W.: Allergy as an Explanation of Dehiscence of a Wound and Incisional Hernia, Arch. Surg. **33**:197 (Aug.) 1936. (*c*) Meleney, F. L., and Howes, E. L.: The Disruption of Abdominal Wounds with the Protrusion of Viscera, Ann. Surg. **99**:5, 1934.

2. Jenkins, H. P.: A Clinical Study of Catgut in Relation to Abdominal Wound Disruption, Surg., Gynec. & Obst. **64**:648, 1937. Hartzell and Winfield.[1a]

3. (*a*) Kraissl, C. J.: Intrinsic Factors Altering the Absorption of Catgut, Surg., Gynec. & Obst. **63**: 561, 1936. (*b*) Maes, U.; Boyce, F. F., and McFetridge, E. M.: Postoperative Evisceration with an Analysis of Forty-Four Cases, Ann. Surg. **100**:968, 1934. (*c*) Glenn, F., and Moore, S. W.: The Disruption of Abdominal Wounds, Surg., Gynec. & Obst. **65**:16, 1937. (*d*) Fallis, L. S.: Postoperative Wound Separation: Review of Cases, Surgery **1**:523, 1936. (*e*) Colp, R.: Disruption of Abdominal Wounds, Ann. Surg. **99**:14, 1934. (*f*) Heyd, C. G.: Disruption of Abdominal Wounds, ibid. **99**:39, 1934. (*g*) Grace, R. U.: Disruption of Abdominal Wounds, ibid. **99**:28, 1934. Hartzell and Winfield.[1a] Meleney and Howes.[1c] Jenkins.[2]

4. Arey, L. B.: Wound Healing, Physiol. Rev. **16**:327, 1936.

5. Carrel, A.: The Process of Wound Healing, Proc. Inst. Med. Chicago **8**:62, 1930.

6. Harvey, S. C.: The Velocity of the Growth of Fibroblasts in the Healing Wound, Arch. Surg. **18**: 1227 (April) 1929.

7. Loeb, L.: A Comparative Study of the Mechanism of Wound Healing, J. M. Research **41**:247, 1919.

8. Smelo, L. S.: The Problem of Wound Healing, Arch. Surg. **33**:493 (Sept.) 1936. Hunt, A. H.: The Role of Vitamin C in Wound Healing, Brit. J. Surg. **28**:436, 1940 Clark, A. H.: The Effect of Diet on the Healing of Wounds, Bull. Johns Hopkins Hosp. **30**:116, 1919. Dann, L.; Glücksmann, A., and Tansley, K.: The Healing of Untreated Experimental Wounds, Brit. J. Exper. Path. **22**:1, 1941. Whipple, A. O.: The Critical Latent or Lag Period in the Healing of Wounds, Ann. Surg. **112**:481, 1940. Howes, E. L., and Harvey, S. C.: Recent Studies in Wound Healing, Yale J. Biol. & Med. **2**:285, 1930; The Clinical Significance of Experimental Studies in Wound Healing, Ann. Surg. **102**:941, 1935. Howes, E. L.; Sooy, J. W., and Harvey, S. C.: The Healing of Wounds as Determined by Their Tensile Strength, J. A. M. A. **92**:42 (Jan. 5) 1929. Hughes, A. F. W., and Dann, L.: Vascular Regeneration in Experimental Wounds and Burns, Brit. J. Exper. Path. **22**:1, 1941. Hertzler, A. E.: The Newer Conception of Wound Healing as Applied to Practical Surgery, Am. J. Surg. **7**:293, 1929.

9. Jenkins.[2] Maes, Boyce and McFetridge.[3b]

10. Baldwin, J. F.: Disruption of Abdominal Wounds, Am. J. Surg. **25**:7, 1934. Kennedy, J. W.: Tragedies of the Abdominal Incision, ibid. **25**:512, 1934. Ramsdell, E. G.: The Prevention of Wound Disruption, South. Surgeon **2**:495, 1940.

11. Localio, S. A.; Casale, W., and Hinton, J. W.: Wound Healing—Experimental and Statistical Study: IV. Results, Surg., Gynec. & Obst. **77**:376, 1943.

opinion that wounds repaired with catgut are more liable to disruption than are wounds repaired with nonabsorbable material, such as silk, silkworm gut or wire, and yet many cases of breakdown of wounds have been reported despite the use of these nonabsorbable materials.[12] In a series of 22 cases reviewed by Glenn and Moore[3c] the incidence of disruption of wounds following closure with catgut was 0.68 per cent, as compared with 0.61 per cent following the use of silk.

As fairly well established causes of disruption or delayed healing of wounds, the following may be listed:[13]

1. Faulty surgical technic or other factors leading to a reduced supply of blood to the healing wound.

2. Inadequate closure of the wound, particularly if this allows for an opening in the peritoneal membrane through which a wedge of omentum may be introduced.

3. Abdominal distention, coughing, violent activity on the part of the patient, etc., in the early postoperative period, leading to actual pulling apart of the margins of the wound.

4. Infection of the wound.

5. Hypoproteinemia.

6. Hypovitaminosis C.

7. Such constitutional states as inanition, cachexia, severe anemia and jaundice.

In an appreciable number of instances, however, none of these factors appears to be operating and yet the wound breaks down or heals poorly. It is for this group that allergy to catgut has been suggested as an important, if not the most important, causative factor. Babcock[14] was one of the first surgeons in this country to consider allergy to catgut seriously as an important causative factor in delayed or abnormal healing of surgical wounds. He stated that allergic reactions to catgut may be due to its major protein constituent (derived from sheep), to unremoved bacterial products or to special toxic substances. In order to avoid an allergic reaction and its untoward effects, he advised the use of silk suture material in all clean wounds. Hinton[1b] demonstrated positive reactions to catgut extract in 9 of 12 patients who had been previously operated on and concluded, ". . . it seems logical to assume that a certain percentage of patients might be considered allergic to catgut." Whipple and Elliott[15] from their studies expressed "little doubt but that the local reaction in patients allergic to catgut predisposes to infection and favors wound disruption." Langston[16] followed 54 patients during the various stages of thoracoplasty and stated that the appearance of the wound was found to reflect directly the severity of the pre-

12. Madelung, O.: Ueber den postoperativen Vorfall von Baucheingeweiden, Arch. f. klin. Chir. **77**:347, 1905. Hartzell and Winfield.[1a]

13. Eliason, E. L., and McLaughlin, C.: Postoperative Wound Complication, Ann. Surg. **100**:1159, 1934. Norris, J. D.: A Review of Wound Healing and the Mechanics of Dehiscence, Surgery **5**:775, 1939. White, W. C.: Disruption of Abdominal Wounds, Ann. Surg. **99**:34, 1934. Sokaloff, S.: Das Aufplatzen der Bauchwunde nach Laparotomie mit Eventration bzw. Freiliegen der Eingeweide, Ergebn. d. Chir. u. Orthop. **25**:306, 1932. Starr, A., and Nason, L. H.: Postoperative Rupture of Abdominal Wounds, J. A. M. A. **100**:310 (Feb. 4) 1933. Milbert, A. H.: A Study of Disruptions of Abdominal Wounds, Arch. Surg. **31**:86 (July) 1935. Glasser, S. T.: Evisceration and Avulsion of Abdominal Wounds, Am. J. Surg. **32**:63, 1936. Freeman, L.: The Cause of Postoperative Rupture of Abdominal Incisions, Arch. Surg. **14**:600 (Feb.) 1927. Clute, H. M.: Abdominal Wound Rupture, S. Clin. North America **8**:123, 1928. Barlett, W.: Pitfalls in Surgery, Surg., Gynec. & Obst. **67**:119, 1938. Thompson, W. D.; Ravdin, I. S., and Frank, I. L.: Effect of Hypoproteinemia on Wound Disruption, Arch. Surg. **36**:500 (March) 1938. Thompson, W. D.; Ravdin, I. S.; Rhoads, J. E., and Frank, I. L.: Use of Lyophile Plasma in Correction of Hypoproteinemia and Prevention of Wound Disruption, ibid. **36**:509 (March) 1938. Ravdin, I. S.: Hypoproteinemia and Its Relation to Surgical Problems, Ann. Surg. **112**:576, 1940. Koster, H., and Shapiro, A.: Serum Proteins and Wound Healing, Arch. Surg. **41**:723 (Sept.) 1940. Harvey, S. C., and Howes, E. L.: Effect of High Protein Diet on the Velocity of Growth of Fibroblasts in the Healing Wound, Ann. Surg. **91**:641, 1930. Smith, A. H., and Moise, T. S.: The Rate of Compensatory Renal Enlargement After Unilateral Nephrectomy in the White Rat, J. Exper. Med. **45**:263, 1927. Lenman, T. H., and Ingals, T. H.: Vitamin C Deficiency and Wound Healing: An Experimental and Clinical Study, Ann. Surg. **105**:616, 1937. Bourne, G. H.: Vitamin C and Repair of Injured Tissue, Lancet **2**:661, 1942. Taffel, M., and Harvey, S. C.: Effect of Absolute and Partial Vitamin C Deficiency on Healing of Wounds, Proc. Soc. Exper. Biol. & Med. **38**:518, 1938. Wolbach, S. B.: Controlled Formation of Collagen and Reticulum: A Study of the Source of Intercellular Substances in Recovery from Experimental Scorbutus, Am. J. Path. **9**: 689, 1933. Menkin, V.; Wolbach, S. B., and Menkin, M. F.: Formation of Intercellular Substance by the Administration of Ascorbic Acid (Vitamin C) in Experimental Scorbutus, ibid. **10**:569, 1934. Wolfer, J. A., and Hoebel, F. C.: The Significance of Cevitamic Acid Deficiency in Surgical Patients, Surg., Gynec. & Obst. **69**:745, 1939. Wolfer, J. A.: Surgical Aspects of Vitamin C Deficiency, S. Clin. North America **20**: 225, 1940. Hartzell and Winfield.[1a] Hinton.[1b] Meleney and Howes.[1c] Jenkins.[2] Maes, Boyce and McFetridge.[3b] Colp.[3e] Grace.[3g]

14. Babcock, W. W.: Catgut Allergy, with a Note on the Use of Alloy Steel Wire for Sutures and Ligatures, Am. J. Surg. **27**:67, 1935.

15. Whipple, A. O., and Elliott, R. E.: The Repair of Abdominal Incisions, Ann. Surg. **108**:741, 1938.

16. Langston, H. T.: The Problem of Catgut Sensitivity and Its Relation to Wound Healing, Ann. Surg. **115**:141, 1942.

operative reaction to the cutaneous test. Bellas [17] reported allergic cutaneous reactions to catgut in some of his patients and was sufficiently impressed by reactions to catgut sutures to say that "incisions heal not because of, but in spite of catgut." From a study of 50 patients in whom disruption of surgical wounds developed Fallis [3d] concluded that "the clinical picture in the noninfective cases suggests an allergic reaction."

Many experimental studies have been made to determine whether or not allergy to catgut is an important cause of disruption of wounds. They have been positive and equally controversial in their results and in the conclusions to which they lead. Marchesani [18] obtained allergic inflammatory reactions to catgut implanted beneath the skin or to catgut extract placed in the conjunctival sac in animals sensitized to catgut and succeeded in demonstrating an antigenic relationship between catgut and sheep serum by anaphylactic studies. In the following year, 1933, Moriconi [19] was unable to confirm these results. He failed to demonstrate allergic inflammation or humoral antibodies in rabbits into which had been injected either plain or iodized catgut. Gratia and Gilson [20] sensitized guinea pigs to sheep serum, to horse serum and to a mixture of these two antigens. After the introduction of strands of catgut or a powdered suspension of catgut intraperitoneally, they stated that the reaction "appears a little less intense in the guinea pigs sensitized to the serum of horse than in those sensitized to the serum of sheep." These reactions were much more intense than those exhibited by normal guinea pigs. Catgut which was soaked in antisheep rabbit serum for a long time provoked but a slight (normal) reaction when implanted into animals sensitized to sheep serum. The authors concluded that catgut is an antigen which will cause an Arthus reaction when introduced into an animal sensitized to sheep serum and stressed what they considered the important relationship of such a reaction to the formation of postoperative adhesions. Frugoni,[21] however, was unable to demonstrate humoral antibodies in rabbits supposedly allergic to catgut, nor could he demonstrate anaphylactins in guinea pigs which had been treated with catgut. After the reintroduction of catgut into the peritoneal cavities of sensitized animals, the only reactions which developed appeared to be nonspecific—responses to foreign material. Kraissl, Kesten and Cimiotti [22] injected into guinea pigs plain catgut, chromicized catgut and chromic acid. Subsequently abdominal incisions were made and repaired with catgut. From 25 to 35 per cent of each of the three groups of sensitized animals had wound disruption, as against none in the control group. Tests to detect cutaneous sensitivity were made on 30 patients who had experienced disruption of wounds, and 19 of these patients gave positive reactions to one or more of the test extracts. More recently, Pickrell [23] was unable to induce a state of hypersensitivity to catgut in rabbits or guinea pigs by repeated injections of ground catgut or by implantation of strands of catgut. He stated: "One can finally conclude that although catgut, like any other suture material, acts as a foreign body and causes slight leukocytic response, it does not act as an antigen to induce the hypersensitive state." In contrast to this Vaccaro and Cabezas [24] reported that catgut does possess antigenic and sensitizing properties and that aseptic inflammation, production of fibrous nodules and adhesions result from the intraperitoneal implantation of catgut in sensitized animals. They found that in such animals absorption of catgut was *delayed*.

The experiments to be described here were designed to determine whether or not a state of hypersensitivity to catgut can be induced and, if so, what effect such hypersensitivity has on the healing of surgical wounds repaired with catgut sutures.

MATERIAL AND METHOD

As a working hypothesis it was considered likely that catgut per se, because of the probable denaturation of protein and the chemical alteration sustained during preparation and because of its relative insolubility, is a poor antigen. It was postulated that sheep serum or sheep intestine might be more effective in stimulating the formation of antibodies to catgut than catgut itself. For these reasons the following materials were used as antigens:

17. Bellas, J. E.: The Influence of Sutures upon Operative Wounds: Review of Cases, Ann. Surg. **112**: 112, 1940.

18. Marchesani, O.: Ueber Catgutanaphylaxie, Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **49**:233, 1932.

19. Moriconi, L.: Ricerca di proprieta antigena del catgut, Rassegna internaz. di clin. terap. **14**:2, 1933.

20. Gratia, A., and Gilson, O.: Le phénomène d'Arthus, au catgut, cause insoupçonnée d'accidents post-opératoires, Mém. Acad. roy. de méd. de Belgique (no. 2) **25**:1, 1934.

21. Frugoni, P.: Sulla supposta allergia da catgut, Arch. ital. di chir. **43**:334, 1936.

22. Kraissl, C. J.; Kesten, B. M., and Cimiotti, J. G.: The Relation of Catgut Sensitivity to Wound Healing, Surg., Gynec. & Obst. **66**:628, 1938.

23. Pickrell, K. L.: Studies on Hypersensitivity to Catgut as a Factor in Wound Disruption, Bull. Johns Hopkins Hosp. **64**:195, 1939. Pickrell, K. L., and Clay, R. C.: Wound Disruption and Catgut Allergy: An Experimental and Clinical Study, Surgery **15**:333 (Feb.) 1944.

24. Vaccaro, H., and Cabezas V., J.: Alergia al catgut y producción de adherencias: Estudio experimental y clínico, Rev. méd. de Chile **70**:750, 1942.

1. Plain surgical catgut (a heterogeneous mixture of remnants collected from the operating room) treated with several changes of acetone and with petroleum benzene (petroleum ether), dried under reduced pressure and ground to a fine powder.

2. Sheep intestine, obtained fresh from the stock yards, thoroughly washed, freed of mucosa and fat, minced, treated with acetone and ether, dried and ground to a fine powder.

3. Sheep serum.

Several extracts of catgut were prepared; the most potent of these was obtained by mixing finely powdered catgut with a tenth-molar solution of sodium hydroxide (15 cc. per gram of catgut), stirring constantly for five minutes, quickly centrifuging and then adding tenth-molar hydrochloric acid to bring the supernatant fluid to a p_H of 7.2 to 7.5. The solution was concentrated by evaporation from a cellophane bag. The final yield was 7 cc. of extract for each gram of powdered catgut used. Although this solution was clear, it gave strongly positive biuret, xanthoproteic and Millon reactions for protein and yielded a heavy precipitate on the addition of tungstic acid.

Thirty-two rabbits and 36 guinea pigs were used in the first part of this study. Rabbits were given multiple subcutaneous and intraperitoneal injections of sheep serum, sheep intestine or catgut, a single dose consisting of 1 to 2 cc. of sheep serum or 80 to 100 mg. of the dried powder made into a heavy suspension with saline solution. Injections were made at intervals of from five days to three weeks. Precipitin titers against sheep serum were determined by the antibody dilution method of Cannon and Marshall,[25] but for those against catgut and sheep intestine solid particles of these antigens were used instead of the usual coated carbon or collodion particles.

EXPERIMENTAL STUDIES

Of three groups of rabbits, each animal received a total of seventeen injections of sheep serum, sheep intestine or catgut over a period of approximately six months, at the end of which time cutaneous tests were performed and antibody titers determined. Cutaneous tests were done after careful preparation of the test sites on the preceding day. Reactions were evaluated at twenty-four hours. In figure 1 the average reaction of each group of rabbits to (*a*) a tiny loop of no. 1 plain catgut implanted subdermally and (*b*) 0.05 cc. of sheep serum injected intradermally is shown. The degree of shading represents the approximate intensity of erythema. The relative size of the lesions was determined by actual measurement. In the same groups of animals (including 6 normal controls) 1 mm. of sterile plain no. 000 catgut,[26] thoroughly washed free of tubing fluid, was inserted into the anterior chamber of the eye. This was accomplished with the animal under pentobarbital sodium anesthesia. A specially prepared 18 gage hypodermic needle and a stylet were used. The point of the needle was introduced into the anterior chamber, just central to the limbus, at 12:30 o'clock, with a minimum of trauma, and the piece of catgut was expelled from the lumen of the needle. Reactions were evaluated at thirty-six hours. Those animals in which traumatic inflammation was severe or in which hemorrhage occurred were discarded from the series. The reactions tended to parallel, roughly, cutaneous reactions to catgut; however, reactions to operative trauma made exact evaluation of allergic inflammation impossible. At three and one-half and seven days the lesions were again carefully examined, but in most instances nonspecific foreign body reactions tended to mask any allergic inflammation that might have been present at this time.

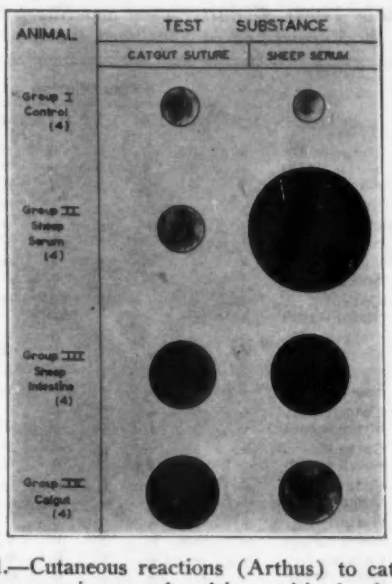

Fig. 1.—Cutaneous reactions (Arthus) to catgut and to sheep serum in normal and in sensitized animals.

Humoral antibody titers against catgut and sheep serum in the various groups are shown in the table. These titers correlate well with the cutaneous reactions previously described. It is apparent that in animals treated only with catgut humoral antibodies for and cutaneous sensitivity to sheep serum develop. A comparison of the relative antibody titers of animals sensitized to sheep serum and of animals sensitized to catgut is shown in figure 2.

From these results one might assume that sheep serum, sheep intestine and catgut are equally effective in stimulating the production of antibodies to catgut; however, in a preliminary experiment, with rabbits, after seven injections of catgut or sheep intestine (compared with seventeen in the present series) a low titer of precipitins against catgut was obtained in each of the animals treated with sheep intestine (3)

25. Cannon, P. R., and Marshall, C. E.: An Improved Serologic Method for the Determination of the Precipitative Titres of Antisera, J. Immunol. **38**:365, 1940.

26. Johnson & Johnson, "Ethicon."

but not in the animals treated with catgut (2). Continued antigenic stimulation in the latter group did lead to the formation of demonstrable humoral antibodies to catgut.

A second series of rabbits (10) was given nine injections of a mixture of sheep serum and powdered sheep intestine subcutaneously during a period of two and one-half months. Of these animals the 2 with the highest humoral antibody titers were selected as donors of serum for passive sensitization of guinea pigs. Pooled serums of these animals agglutinated particles coated with sheep serum at a dilution of 1 : 1,920 (highest dilution used) and carbon particles coated with catgut extract at a dilution of 1 : 240. Complement-fixing antibodies for this catgut

Precipitin Titers Against Catgut and Sheep Serum in Normal and in Sensitized Rabbits

Animal	Antigen	Serum Dilution 1:20	1:40	1:80	1:160	1:320	1:640	1:1280
1 control	Catgut.....	0	0	0	0	0	0	0
	Sheep serum	0	0	0	0	0	0	0
2-s.s.	Catgut.....	+	+	+	0	0	0	0
	Sheep serum	+	+	+	+	+	+	0
3-s.s.	Catgut.....	+	+	+	0	0	0	0
	Sheep serum	+	+	+	+	+	+	0
4-s.s.	Catgut.....	+	+	+	0	0	0	0
	Sheep serum	+	+	+	+	+	+	0
5-s.s.	Catgut.....	+	+	+	0	0	0	0
	Sheep serum	+	+	+	+	+	+	0
6-s.i.	Catgut.....	+	+	+	+	0	0	0
	Sheep serum	+	+	+	+	+	0	0
7-s.i.	Catgut.....	+	+	+	0	0	0	0
	Sheep serum	+	+	+	+	+	0	0
8-s.i.	Catgut.....	+	+	+	0	0	0	0
	Sheep serum	+	+	+	+	+	0	0
9-cg.	Catgut.....	+	+	+	+	+	0	0
	Sheep serum	+	+	0	0	0	0	0
10-cg.	Catgut.....	+	+	+	0	0	0	0
	Sheep serum	+	+	+	+	0	0	0
11-cg.	Catgut.....	+	+	+	0	0	0	0
	Sheep serum	+	+	+	+	0	0	0
12-cg.	Catgut.....	+	+	+	0	0	0	0
	Sheep serum	+	+	+	+	0	0	0

extract were also demonstrated. Guinea pigs (200 to 250 Gm.) were given three doses of this pooled anticatgut rabbit serum intraperitoneally, (1.5 cc. in each dose) at twelve hour intervals. Four days after the first dose of serum, each of the animals was given, via the jugular vein, 1 cc. of an extract of plain catgut. Each of the 3 sensitized pigs gave a slight but definite anaphylactic reaction, characterized by ruffing of hair, dyspnea, wheezing and slight to moderate prostration. Two normal control animals gave no reaction following similar treatment. The catgut extract used in this particular experiment was weak, which fact may explain the survival of the shocked, sensitized pigs. Guinea pigs of a second group (150 to 180 Gm.), virgin females, were passively sensitized as was the preceding group (they received 3 cc. instead of 4.5 cc. of antiserum). At four days smooth muscle strips (uterine horns) were obtained for in vitro anaphylactic studies. The horns of each sensitized animal gave a typical anaphylactic reaction to either sheep serum or catgut extract, as compared with the insignificant reactions obtained with control strips (fig. 3).

From these observations it is apparent that hypersensitivity to catgut has been produced and that there is a definite antigenic relationship between sheep serum, sheep intestine and catgut.

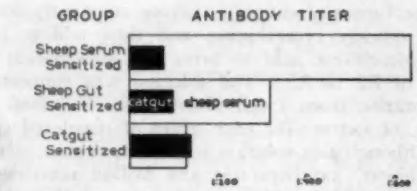

Fig. 2.—Antigenic relationship between catgut and sheep serum as demonstrated by antibody reactions in rabbits sensitized to sheep serum, to sheep intestine and to catgut.

The question arises, however, as to the nature of this antigenic relationship. Is sheep serum protein the only antigenic constituent of catgut, or does catgut possess, in addition, some antigenic substance not present in sheep serum? To answer this question, two groups of 6 guinea pigs (150 to 180 Gm.) were given subcutaneous injections, one group receiving 0.3 cc. of sheep

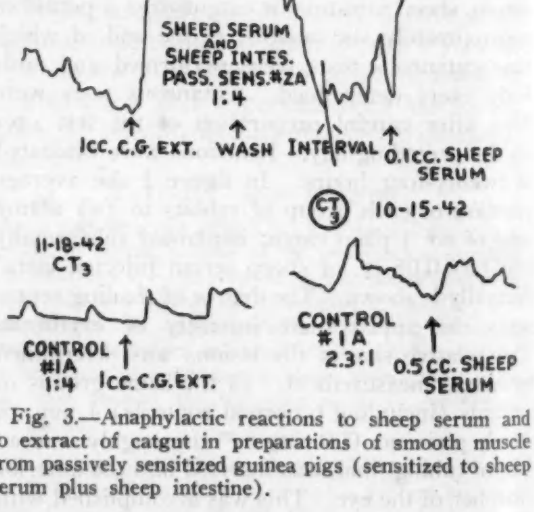

Fig. 3.—Anaphylactic reactions to sheep serum and to extract of catgut in preparations of smooth muscle from passively sensitized guinea pigs (sensitized to sheep serum plus sheep intestine).

serum and the other group 50 mg. of powdered catgut suspended in saline solution. Three doses were given at three day intervals. Four weeks after the first injection, uterine horns were obtained for anaphylactic studies. One horn of each sensitized animal was tested with the specific substance with which the animal had been treated

in order to ascertain a state of hypersensitivity. Every animal gave a positive reaction. The remaining horn was treated with the other antigen, either sheep serum or catgut extract, as the case might be. In each instance an anaphylactic reaction was obtained on first exposure to this antigen. This treatment was repeated several times, with washing of the horn and an interval for recovery in between, until with the horns of the animals sensitized to catgut sheep serum no longer gave an anaphylactic reaction. In other words, antibodies specific for sheep serum in these animals sensitized to catgut had been completely exhausted. Subsequently, the strips were exposed to catgut extract, and, as illustrated in figure 4, a typical anaphylactic reaction resulted. These results demonstrate that at least two groups of antibodies are elicited as a result of antigenic stimulation by catgut, one of which will react with both sheep serum and catgut and the other of which is specific for catgut. The converse of this was not established. After as many as eleven reactions to catgut extract, the uterine strip of an animal sensitized to sheep serum was still capable of slight anaphylactic response on a twelfth exposure to catgut extract, after which this strip exhibited an anaphylactic reaction (diminished) to sheep serum also. From these results it was concluded that the most likely antigenic relationship between catgut and sheep serum is that shown in figure 5.

From Dr. Francis O. Schmitt [27] highly purified preparations of sheep collagen were obtained for testing with the anticatgut rabbit serum previously described, to determine whether or not antibodies specific for collagen could be demonstrated. Some technical difficulty was encountered in preparing particles of optimum size from this substance for the determination of precipitin titers; however, one of the samples, "of very high purity," was agglutinated by anticatgut serum at a dilution of 1:80. A second sample, described as being of the "highest purity," having been treated by enzymes in the final stages of preparation, was not agglutinated by serum at a dilution of 1:10. It is possible that in this second preparation of collagen enzymatic action altered antigenic constituents which may have been present. It is also possible that the positive reactions with the one sample of collagen might have been the result of some impurity (sheep serum protein).

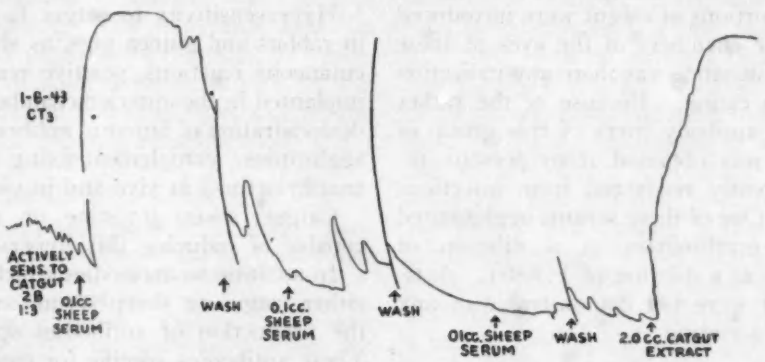

Fig. 4.—Anaphylactic reaction to extract of catgut in a preparation of uterine horn from a guinea pig actively sensitized to sheep serum. During the course of the three exposures to sheep serum, antibodies specific for sheep serum were exhausted.

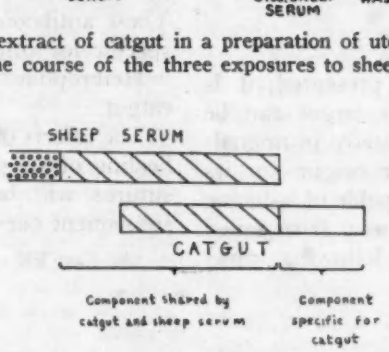

Fig. 5.—Probable antigenic relationship between catgut and sheep serum.

With the demonstration that antigens from sheep serum are present in catgut, the possibility arose that perhaps antigens of sheep erythrocytes might also be present and that, since sheep erythrocytes are an excellent source of heterophile antigen, there might be some relationship between heterophile antibodies and antibodies for catgut. Such a relationship, if it existed, might be of importance, since approximately 4 per cent

27. Of the Department of Biology and Biological Engineering, Massachusetts Institute of Technology.

of human beings normally possess heterophile antibodies in their blood and since during certain conditions, notably infectious mononucleosis, the heterophile antibody titer reaches a high level. It was thought that these heterophile antibodies might provide a mechanism by which persons could become hypersensitive to catgut without ever having contacted this substance or without having a manifest allergy to sheep serum. To investigate this possibility rabbits were given repeated injections of heterophile antigen (a sterile emulsion of guinea pig kidney) over a period of several months until a maximum titer of 1:480 was obtained against washed sheep erythrocytes. Cutaneous tests with catgut were made and precipitin titers against catgut determined as before. Also, portions of catgut were introduced into the anterior chambers of the eyes of these animals. In no instance was there any indication of sensitivity to catgut. Because of the rather low heterophile antibody titers of this group of rabbits, serum was obtained from persons recovering or recently recovered from infectious mononucleosis. One of these serums agglutinated washed sheep erythrocytes at a dilution of 1:1,920 (others at a dilution of 1:480). Antibodies to catgut were not demonstrable in any of these human serums.

COMMENT

From the experiments here presented, it is evident that hypersensitivity to catgut can be consistently produced experimentally in animals and that either sheep serum or catgut (or its antecedent, sheep intestine) is capable of inducing this state. Some investigators may have failed to induce sensitivity in animals following injection of catgut because too little of this substance was used and/or because the period of treatment was too short. It will be recalled that as much as 700 mg. of finely powdered catgut administered over a period of one and one-half months failed to stimulate demonstrable humoral antibodies to catgut, whereas 1,700 mg. of this substance given over a six month period did induce hypersensitivity (1,700 mg. of catgut [dry weight] represents a 915 cm. length of size no. 0 plain catgut). The effects of hypersensitivity to catgut on the healing of surgical wounds repaired with catgut sutures will be the subject for analysis in a subsequent paper.

SUMMARY AND CONCLUSIONS

Hypersensitivity to catgut has been produced in rabbits and guinea pigs, as shown by positive cutaneous reactions, positive reactions to catgut implanted in the anterior chamber of the eye and demonstration of humoral antibodies (precipitins, agglutinins, complement-fixing antibodies and anaphylactins) in vivo and in vitro.

Catgut, sheep intestine or sheep serum is capable of inducing this hypersensitive state.

In addition to antibodies which will react with either catgut or sheep serum, catgut stimulates the production of antibodies specific for itself. These antibodies specific for catgut may also be specific for collagen or for mucoprotein.

Heterophile antibodies do not react with catgut.

The effects of hypersensitivity to catgut on the healing of surgical wounds repaired with catgut sutures will be the subject for analysis in a subsequent paper.

950 East Fifty-Ninth Street.

ROLE OF ALLERGY IN DELAYED HEALING AND IN DISRUPTION OF WOUNDS

II. EFFECT OF SPECIFIC SENSITIVITY TO CATGUT ON REACTION OF TISSUES TO CATGUT SUTURES AND ON HEALING OF WOUNDS IN THE PRESENCE OF CATGUT SUTURES

HOWARD C. HOPPS, M.D.
CHICAGO

In a previous report [1] the general problem of delayed healing and disruption of wounds was discussed and experimental evidence was given to support the fact that hypersensitivity to catgut can be produced in animals by adequate antigenic stimulation. The experiments to be described in this paper were designed to evaluate the effects of such hypersensitivity on the reaction of tissues to catgut sutures and on the healing of surgical wounds repaired with catgut.

MATERIAL AND METHOD

Eighty-eight rabbits were used in this study. Plain and chromicized catgut, sizes no. 0 and no. 1, were used throughout the experiments. In all operative procedures the technics commonly used in surgical practice were employed to maintain asepsis. Operative sites were carefully prepared by shaving, scrubbing with soap and water and thoroughly cleansing with a solution of 1 per cent iodine in 70 per cent alcohol. Laparotomies were done with the animals under pentobarbital sodium anesthesia. The incisions were paramedian and 8 cm. long, extending 2 cm. from the pubis. These wounds were carefully closed in three layers with no. 0, plain, nonboilable catgut,[2] which had been thoroughly washed free of tubing fluid in several changes of sterile isotonic solution of sodium chloride. Abdominal wounds were covered with massive sterile dressings and a binder, which in most instances were left in position until the fourth postoperative day. A second type of operation was done in which single strands of catgut were implanted into the pectoralis major or the trapezius muscle of rabbits. An initial small cutaneous incision was made to expose the muscle. The catgut was implanted in the form of a loose loop, which was firmly tied, and the cutaneous incision (which did not directly overlie the catgut) was closed with metal wound clips. No dressing was applied. All biopsy specimens were fixed in Zenker's fluid, embedded in celloidin, cut into sections 10 to 16 microns thick and stained with hematoxylin and eosin.

EXPERIMENTAL STUDIES

In five series of rabbits, catgut was implanted into muscle as described. In these series were included 18 normal rabbits, 10 sensitized to sheep serum, 19 sensitized to sheep intestine, 16 sensitized to catgut and 6 immunized against heterophile antigen. In all of these treated animals, with the exception of those immunized against heterophile antigen, precipitins to catgut had been demonstrated. Titers ranged from 1:20 to 1:640, with an average of about 1:100, by the antibody dilution method. From one to three strands of catgut were implanted at operation. Biopsies were made at intervals of from one to five days. A total of 142 such biopsy specimens was studied. Although considerable variation in the reaction of tissue to suture material was evident within each group, among the groups taken as a whole there was no significant variation in the reactions at one, two, three and a half or five days to either plain or chromicized catgut.[3] Average reactions to catgut at two days are shown by the photomicrographs in figure 1.

From these results it appeared unlikely that allergic reaction to catgut was a significant factor in the pathogenesis of disruption of wounds. It was considered advisable, however, to produce abdominal wounds in animals sensitized to catgut and in normal animals, repair these wounds with catgut sutures and observe the course of their healing over a sufficient period to allow for disruption, if that was going to occur. This was done with 10 normal rabbits and 9 rabbits which had received multiple injections of a mixture of sheep serum and finely powdered sheep intestine over a period of two and one-fourth months. In the latter group antibodies to catgut and to sheep serum had been demonstrated. Abdominal wounds were produced as previously described and carefully inspected at four, seven and nine days postoperatively. One sensitized animal showed slight focal erythema of the margins of the wound, and another exhibited moderate induration about one of the sutures. In neither of these was there any apparent effect on the normal rate of healing. A third sensi-

From the Department of Pathology, University of Chicago.

1. Hopps, H. C.: The Role of Allergy in Delayed Healing and in Disruption of Wounds: I. Antigenicity of Catgut, Arch. Surg., this issue, p. 438.

2. Johnson & Johnson, "Ethicon."

3. Davis and Geck, "Thermoflex" nonboilable, plain no. 1 catgut; Johnson & Johnson, "Ethicon" nonboilable, plain no. 0 catgut; Scannlin, twenty day chromic no. 1 catgut.

tized animal dislodged his abdominal dressing on the second postoperative day and traumatized the wound so that there was a partial separation of the skin. At nine days, from each of these animals a biopsy specimen was taken through the entire thickness of the abdominal wall to include a portion of the incision and a portion of the suture material. At this time inspection was made of the peritoneal surfaces of the wounds, and all appeared to be in a good state of repair. On histologic study of these tissues particular attention was given to general reactions (inflammatory, proliferative and degenerative), fibroplasia, reaction to suture material, state of the sutures (decrease in size, fragmentation, etc.), edema and presence of fibrin. These were estimated in a rough quantitative fashion and tabulated. There were no significant differences in these points between the two groups, and in all animals the suture material was well preserved (fig. 2). There was one change in 2 of the sensitized group, however, which was not present in any control animal, a change manifested by small, circumscribed granulomatous lesions, which closely resembled proliferating tubercles. One of the 2 sensitized animals showed a single such

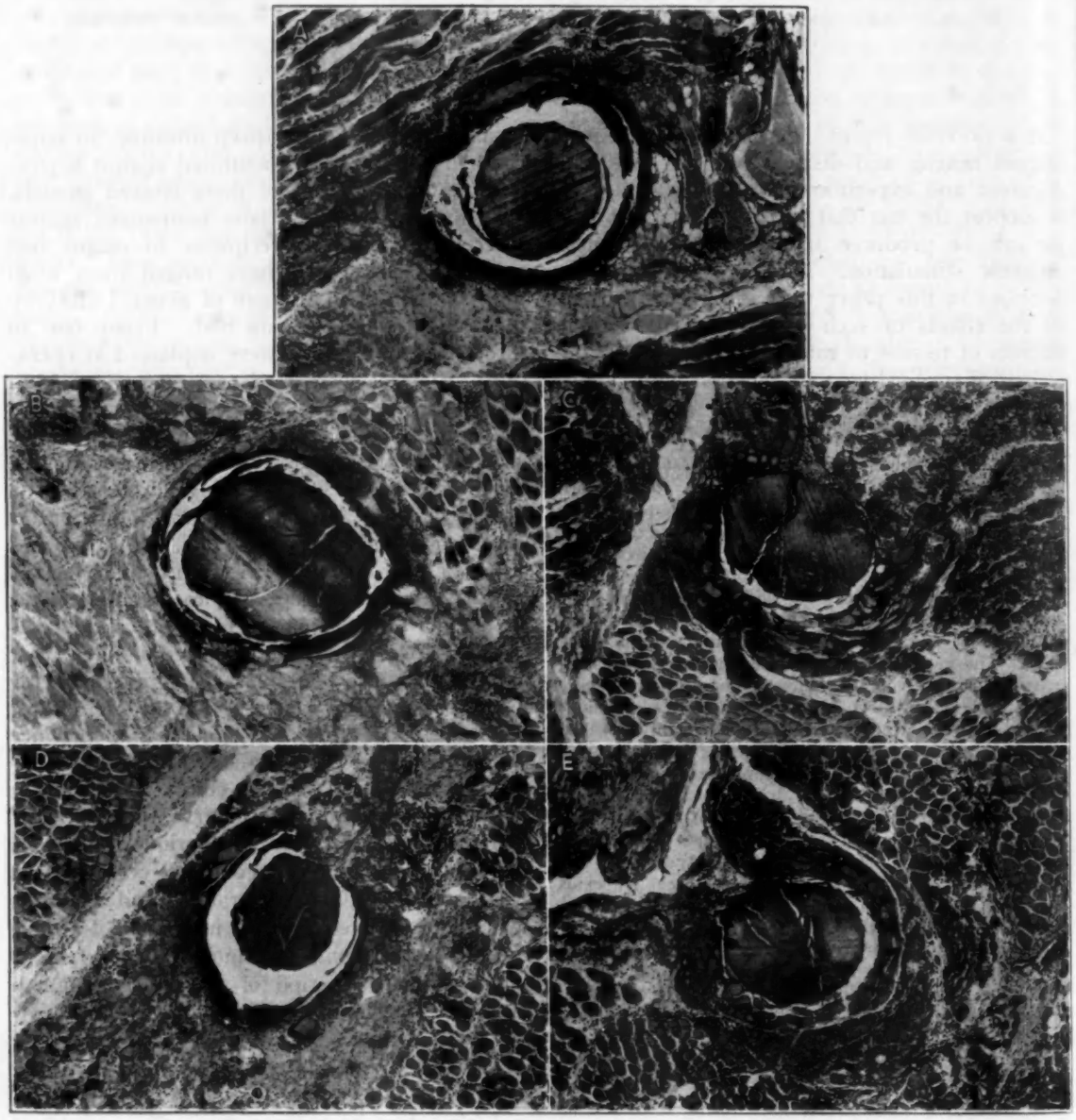

Fig. 1.—Photomicrographs (× 38) showing average reaction to catgut sutures at two days in rabbits: *A*, normal; *B*, sensitized to sheep serum; *C*, sensitized to sheep intestine; *D*, sensitized to catgut; *E*, sensitized to heterophile antigen (stained with hematoxylin and eosin).

lesion (fig. 3), and the other exhibited several smaller but otherwise similar foci. No nidus of foreign material was evident in any of these tuberculoid nodules, nor did they resemble the occasional focal lesions which were definitely related to foreign body particles.

COMMENT

Catgut is antigenic, and sufficient sensitivity can be established to it so that a weakly positive Arthus reaction can be elicitied from implantation of a strand of this material subdermally

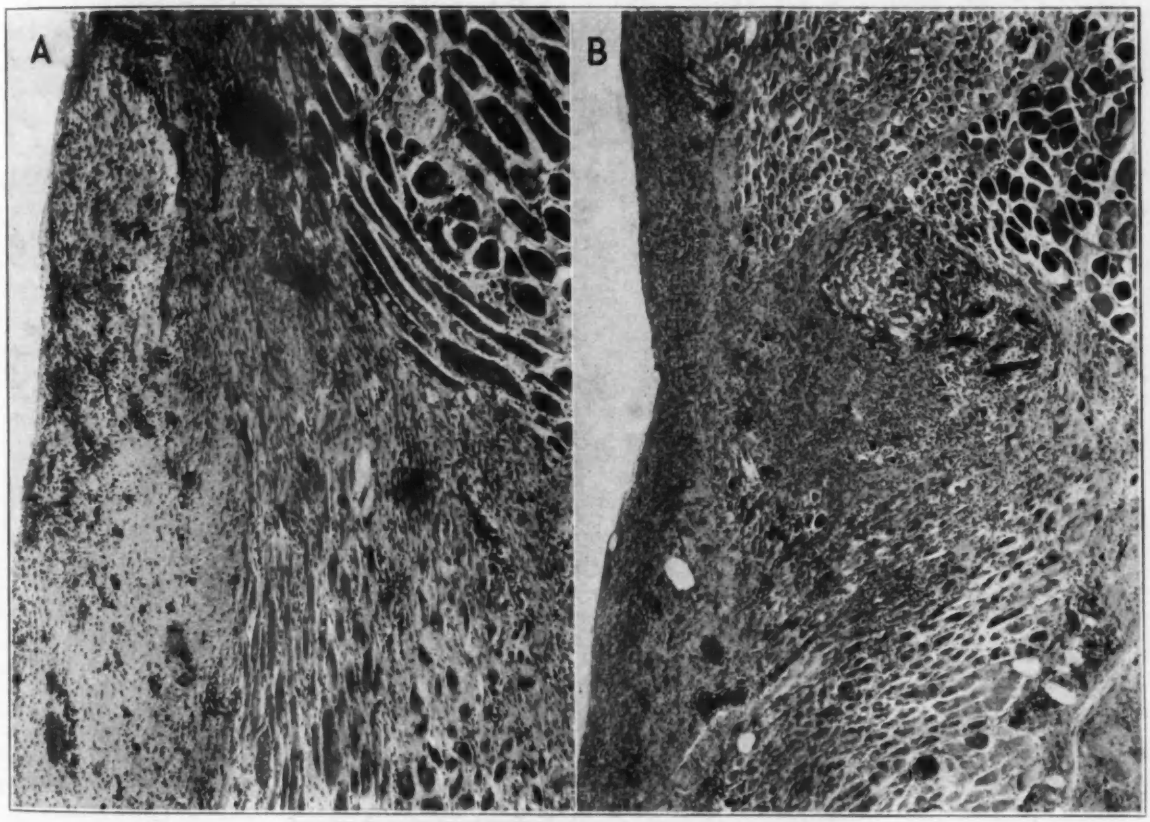

Fig. 2.—Photomicrographs (× 56) of healing wounds nine days after operation in rabbits: *A*, normal; *B*, hypersensitive to catgut. The free margin represents the peritoneal surface (stained with hematoxylin and eosin).

or into the anterior chamber of the eye.[1] In spite of this, however, disruption or appreciably delayed healing of wounds does not occur when animals sensitized to catgut are operated on and their wounds repaired with catgut sutures. The apparent paradox between the presence of humoral antibodies to catgut and the failure of tissues of specifically sensitized animals to give rise to allergic inflammation on contact with catgut probably rests on the fact that catgut is relatively insoluble. It is well known that catgut sutures may persist in the tissues for weeks or even months.[4] This relative insolubility is well demonstrated by a simple experiment in which finely powdered catgut is treated with a 5 per cent solution of sodium chloride and constantly stirred for four hours at a p_H of 4.5 or 8, and the supernatant is concentrated ten times by evaporation from a cellophane bag and tested for protein. A faintly positive biuret reaction is obtained only after a delay of approximately thirty minutes. A situation analogous to this was brought out by Dr. Taliaferro in his discussion of antigen-antibody reactions to metazoan parasites.[5] He stated: "The powdered cuticle of Ascaris lumbricoides var. serum is highly antigenic and serum from infected rabbits exhibits a high anticuticle precipitin content . . . but these antibodies do not react with the cuticle of the larvae [*in the tissues of sensitized animals*] because of the insolubility of the cuticle in the living worm."

It has been stated by various observers that the absorption of catgut is greatly increased in

4. Feriz, H.: Catgut and Collagen, Surgery **10**:326, 1941.

5. Taliaferro, W. H.: Antigen-Antibody Reactions in Immunity to Metazoan Parasites, Proc. Inst. Med. Chicago **14**:358, 1943.

certain persons. Heyd [6] spoke of a type of person in whom catgut may be completely dissolved before the tensile strength of the wound is sufficient to maintain closure. Hinton [7] referred to the "warning note by all authors as to the peculiar capacity of the tissues of some persons to digest catgut completely." Kraissl [8] reported that of 56 cases of disruption of wounds, in every case in which the appearance of the sutures was described (19) they were observed to be completely or almost completely digested. Langston [9] described a case of such digestion of sutures in a patient who gave a positive reaction to a cutaneous test with catgut extract. In a discussion of factors which determine the loss of strength of catgut when embedded in tissue, Howes [10] stated that in the presence of fluids such as isotonic solution of sodium chloride or blood serum the tensile strength of catgut is moderately diminished and that in an inflammatory exudate catgut, either plain or chromicized, loses tensile strength rapidly. However this may be, in rabbits with demonstrable hypersensitivity to catgut absorption of catgut sutures in the tissues is not increased appreciably during the critical period of healing of the wound. This observation is substantiated by the recent studies of Vaccaro and Cabezas,[11] who demonstrated that in rabbits and guinea pigs which had been sensitized to sheep serum or catgut, absorption of catgut implanted into the peritoneal cavity was *delayed*.

Fig. 3.—Photomicrograph (× 56) showing a tuberculoid lesion in a healing wound of a rabbit sensitized to catgut nine days after operation (stained with hematoxylin and eosin).

It may appear difficult to reconcile this fact with the demonstration that rabbits sensitized to catgut manifested a positive Arthus reaction

6. Heyd, C. G.: Disruption of Abdominal Wounds, Ann. Surg. **99**:39, 1934.

7. Hinton, J. W.: Allergy as an Explanation of Dehiscence of a Wound and Incisional Hernia, Arch. Surg. **33**:197 (Aug.) 1936.

8. Kraissl, C. J.: Intrinsic Factors Altering the Absorption of Catgut, Surg., Gynec. & Obst. **63**:561, 1936.

9. Langston, H. T.: The Problem of Catgut Sensitivity and Its Relation to Wound Healing, Ann. Surg. **115**:141, 1942.

10. Howes, E. L.: Factors Determining the Loss of Strength of Catgut When Imbedded in Tissue, J. A. M. A. **90**:530 (Feb. 18) 1928.

11. Vaccaro, H., and Cabezas, V. J.: Alergia al catgut y producción de adherencias: Estudio experimental y clínico, Rev. méd. de Chile **70**:750, 1942.

to catgut implanted subdermally.[1] It will be recalled, however, that such a reaction was slight and characterized principally by erythema. It is logical to assume that the slight cutaneous reactions which were observed in the abdominal wounds of 2 sensitized animals, as previously described, represent a similar degree of allergic reaction and that the tuberculoid lesions described in the deeper tissues of several of the wounds also indicate an altered response to catgut by rabbits hypersensitive to catgut. The allergic inflammatory reaction to catgut implanted into the anterior chambers of the eyes of specifically sensitized rabbits is somewhat different. There the suture material is in a fluid medium and, according to Howes, susceptible to more rapid dissolution than could be expected in sterile solid tissue. Although Hektoen and Carlson [12] showed that the aqueous normally contains few antibodies even in an animal with a high humoral antibody titer, any procedure by which large particles of foreign material are introduced into this chamber should afford sufficient trauma to allow for a considerable increase in permeability of the encapsulating membrane and a ready entrance of antibody protein.

12. Hektoen, L., and Carlson, A. J.: On the Distribution of Antibodies and Their Formation by the Blood, J. Infect. Dis. **7**:319, 1910.

It is possible that under certain conditions in which the solution of catgut sutures in tissues is greatly accelerated a significant allergic inflammatory reaction might result if the affected person were hypersensitive to catgut. Under such circumstances, however, the hastened absorption of suture material with accompanying loss of tensile strength would represent the primary defect and would probably be sufficient basis in itself for disruption of the wound.

SUMMARY AND CONCLUSIONS

In animals which are hypersensitive to catgut, evidence of slightly heightened reaction of the tissues to catgut sutures has been observed.

There is no appreciable difference between normal rabbits and rabbits sensitized to catgut in the rate of dissolution or digestion of catgut sutures during the critical period of healing of wounds.

There is no significant difference between normal rabbits and rabbits sensitized to catgut in the healing of laparotomy wounds repaired with catgut sutures.

The absence of significant allergic reaction to catgut in the wounds of animals sensitized to catgut is attributed to the relative insolubility of catgut sutures.

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ROLE OF ALLERGY IN DELAYED HEALING AND IN DISRUPTION OF WOUNDS

III. DELAYED HEALING AND DISRUPTION PRODUCED BY LOCAL ALLERGIC REACTION (AUER PHENOMENON)

HOWARD C. HOPPS, M.D.
CHICAGO

Local anaphylaxis has been suggested as a mechanism which provokes disruption or delayed healing of surgical wounds. Catgut sutures have been considered the offending allergen in such instances. As a direct effect of antigen-antibody reaction within the wound, premature dissolution of catgut and/or increased inflammatory reaction have been postulated. In a preceding study,[1] evidence was presented to show that premature dissolution of catgut or significant inflammatory response does not occur in the tissues of specifically sensitized animals on contact with catgut, because of the relative insolubility of this material. The effect of local anaphylactic reaction within the tissues of a healing wound thus remains to be investigated. In order to determine this effect, a new mechanism was sought, one by which a local concentration of *soluble* antigen and specific antibody at the site of the healing wound could be effected.

Auer,[2] in 1920, first demonstrated that at the site of an early mild inflammatory reaction a massive severe inflammation could be superimposed by parenteral administration of a large dose of antigen to a specifically sensitized animal. He produced severe inflammatory reactions and necrosis in the ears of rabbits sensitized to horse serum by gently rubbing the ears with xylene and then injecting 10 cc. of horse serum intraperitoneally. Auer described this reaction as "local autoinoculation of the sensitized organism with foreign protein" and attributed the resultant inflammatory response to a primary, local anaphylactic reaction. He expressed the opinion that this reaction was a variation of the Arthus phenomenon, differing from it, for one thing, in that "the sensitized animal reinjects itself where there are inflammation and edema, providing that some of the antigen is circulating, the amount being so dilute that it is ineffective under ordinary conditions." In recent studies on the mechanism of the Arthus reaction, by Cannon and Marshall,[3] it has been demonstrated that this phenomenon is related definitely to the presence of precipitins in the blood and that the intensity of such a local anaphylactic reaction parallels the precipitin content of the blood. If it is admitted that the phenomenon of Arthus and that of Auer are analogous, it becomes necessary to go one step further than Auer did in explaining the mechanism by which local anaphylaxis occurs. It must be assumed that not only is antigen concentrated locally in the area of primary inflammation, but antibody, from the blood, is concentrated there as well.

Inasmuch as a fresh surgical wound represents a focus of early acute inflammation, it was considered that under proper conditions circulating antigen and antibody might localize there. A quotation from the introductory paragraph of Auer's paper on local anaphylaxis is of special significance in this respect. "While testing the sensitiveness of a number of dogs which had been treated with horse serum some years previously, and employing heavy doses of horse serum for the reinjections, it was observed that a peculiar edema developed at the site of the operation wound in the inguinal region. This edema was noted about two days after the test and formed a fairly extensive, thick, brawny mass of tissue."

It is generally accepted that disruption of the wound is more prone to occur when an abdominal operation is done in the face of preexisting infection, such as pelvic abscess or peritonitis. Although this increased incidence of breakdown of the wound may be in response to direct infection of the wound, the possibility of yet another mechanism appears. In the presence of a well localized infection, the patient may be assumed

From the Department of Pathology, University of Chicago.

1. Hopps, H. C.: Role of Allergy in Delayed Healing and in Disruption of Wounds: II. Effect of Specific Sensitivity to Catgut on Reaction of Tissues to Catgut Sutures and on Healing of Wounds in the Presence of Catgut Sutures, Arch. Surg., this issue, p. 445.

2. Auer, J.: Local Autoinoculation of the Sensitized Organism with Foreign Protein as a Cause of Abnormal Reactions, J. Exper. Med. **32**:427, 1920.

3. Cannon, P. R., and Marshall, C. E.: Studies on the Mechanism of the Arthus Phenomenon, J. Immunol. **40**:127, 1941.

to have a rather high degree of immunity or sensitivity to the specific infectious agent and a high humoral antibody titer. As the result of operative manipulation of such a localized infectious lesion, an appreciable amount of dead or living bacteria and their products may be forced through the protective barrier of granulation tissue to enter the general circulation. Under these conditions, all of the necessary requirements for the development of an Auer reaction would be fulfilled: (1) the surgical wound, providing a localizing lesion; (2) the chronic infection, stimulating a high humoral and tissue antibody titer, and (3) manipulation of the localized infectious process, allowing for the introduction of specific antigen into the blood stream. To test this hypothesis, the following experiments were done.

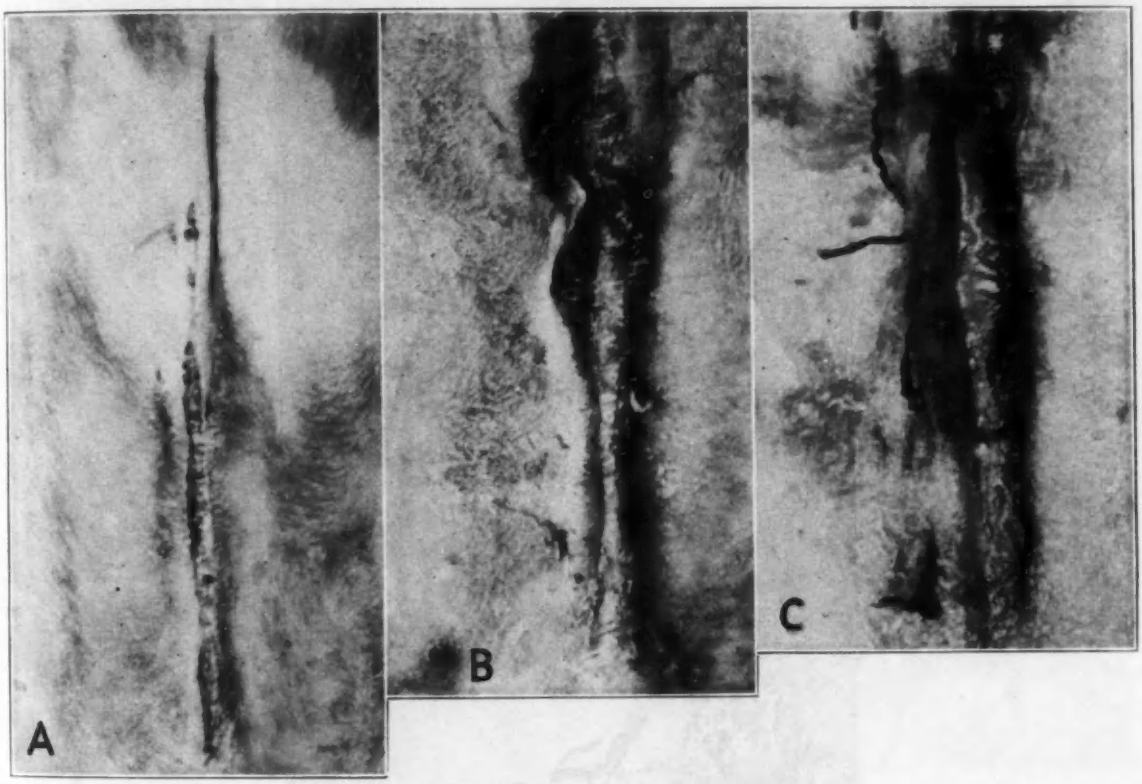

Fig. 1.—Photographs illustrating the gross appearance of abdominal wounds at seven days in (*A*) normal rabbit and (*B* and *C*) 2 rabbits sensitized to horse serum. Each animal received horse serum intravenously immediately after the operation. Note that for the animal in *C* silk was the suture material used. (An interrupted horizontal mattress stitch was used to close the cutaneous layer.)

MATERIAL AND METHOD

Sixty-one rabbits were used in this study. Rabbits were sensitized to either horse serum or crystalline egg albumin by multiple intramuscular injections of these substances adsorbed on aluminum hydroxide gel, after the method of Hektoen and Welker,[4] with additional subcutaneous injections of horse serum or 1 per cent solution of egg albumin. A high degree of sensitivity was produced, as demonstrated by strongly positive cutaneous reactions (Arthus) and by high precipitin titers of the serums, averaging 1:1,500 in either group, as determined by the antibody dilution method of Cannon and Marshall.

Abdominal operations were performed under strict aseptic precautions in the same manner as described in preceding experiments.[1] The abdominal wounds were paramedian and 8 cm. long. They were carefully closed in three layers either with plain, no. 0, nonboilable catgut[5] from which tubing fluid had been thoroughly washed or with silk. Wounds were covered with massive sterile dressings and tight binders, which were left intact until the fourth postoperative day. Ten cubic centimeters of 0.35 per cent egg albumin or 10 cc. of 35 per cent horse serum (in saline solution) was injected into the marginal vein of the ear over a period of fifteen to thirty minutes immediately after operation to specifically sensitized and to control animals.

Biopsy specimens were fixed in Zenker's fluid, embedded in celloidin and sectioned at 10 to 16 microns. Sections were stained with hematoxylin and eosin, and also with a combination of Bielschowsky's silver impregnation method with Hansen's modification of Van Gieson's stain for collagen.

4. Hektoen, L., and Welker, W. H.: Precipitin Production in Rabbits Following Intramuscular Injection of Antigen Adsorbed by Aluminum Hydroxide, J. Infect. Dis. **53**:309, 1933.

5. Johnson & Johnson "Ethicon" suture.

EXPERIMENTAL STUDIES

Laparotomy wounds were made in 37 rabbits. Sixteen of these animals had been sensitized to horse serum and 15 to crystalline egg albumin in the manner described. Six were normal animals. Of these 31 sensitized animals, 25 received specific antigen intravenously after operation. The remaining 6 received foreign protein (egg albumin or horse serum) other than that to which they were hypersensitive. The 6 normal rabbits received egg albumin or horse serum also. Thus, within the control group of 12 rabbits any nonspecific effects attributable to a state of hypersensitivity or to the introduction of foreign protein could be determined.

Twelve of the sensitized rabbits receiving specific antigen died of anaphylactic shock. An additional animal was discarded from this series because of infection of the wound. Of the remaining 11 animals, in 2 frank separation of the upper layers of the wound developed (without actual evisceration) and 7 exhibited gaping of the margins of the skin. In 2 animals an untoward reaction was limited to induration and hyperemia of the margins of the wound. Most of the animals of this group exhibited edema and hyperemia of the margins of the wound and a moderate degree of serosanguineous exudation. It is of special interest that, of the 3 animals whose wounds were repaired with silk sutures, in 1 separation of the upper layers of the wound developed and in another there was gaping of the margins of the skin (fig. 1). In this group the reactions of the animals sensitized to horse serum and of those sensitized to egg albumin were essentially similar. The intensity of the reactions tended to parallel the precipitin titers of the serums, which varied from 1:960 to 1:1,920. Of 12 control animals, infection of the wound developed in 1 and another dislodged its abdominal dressing and traumatized the wound, with resultant partial separation of the cutaneous layer. In the remaining 10 controls, separation of the layer of skin developed in only 2, and over but a portion of the wound. These 2 animals did not exhibit the degree of edema and hyperemia seen in the specifically sensitized group, nor was there serosanguineous discharge from their wounds.

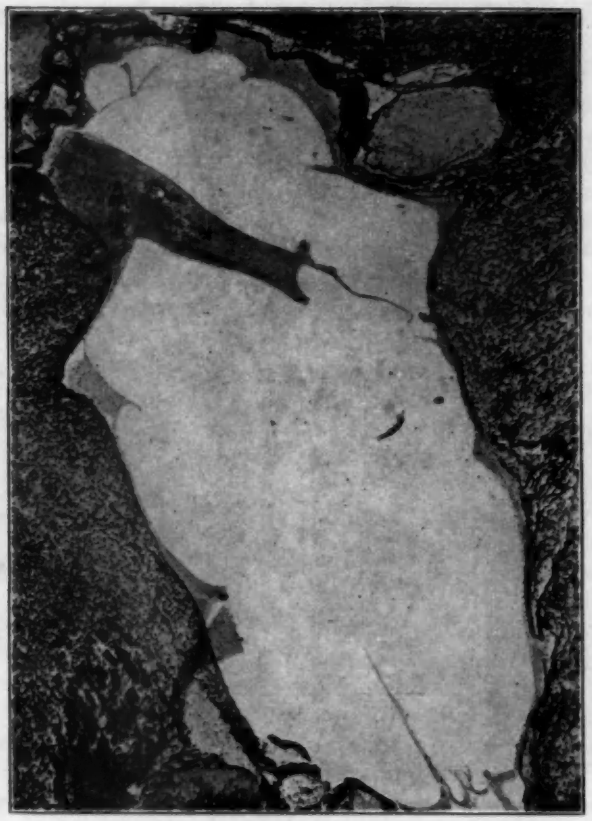

Fig. 2.—Photomicrograph (× 40) showing the appearance of the margins of the wound (deep) at nine days in a rabbit sensitized to horse serum which was given horse serum intravenously immediately after the operation. (Stained with hematoxylin and eosin.)

Nine days after operation, biopsy specimens were taken through the wounds at right angles to the plane of incision and the tissues prepared for microscopic examination. Tissues were carefully studied with special consideration of the following points: general reaction (inflammatory, proliferative and degenerative), degree of fibroplasia, reaction to sutures, state of sutures (intact, fragmented, etc.), edema and presence and extent of deposition of fibrin. In 4 of the 11 sensitized animals which received specific antigen after operation, there was evident frank separation of the margins of the wound in the deeper layers of tissue (fig. 2). This was observed in none of the controls, although in 2 animals there was separation of muscle from subcutaneous tissue in a plane parallel to the surface of the skin. There was no significant difference between the two groups of animals in the reaction to the sutures or in the state of the sutures, and, surprisingly, no appreciable difference in the degree of general inflammatory reaction in the plane of incision or in the amount of edema present in the intact portions of tissue. On examination of the area of incision under low magnification, the number of inflammatory cells appeared about the same in the two groups of animals. On closer scrutiny, however, it was seen that the types of inflammatory cells present differed significantly; the ratio of macrophages to fibroblasts was considerably greater in the animals into which specific antigen had been injected after operation. In biopsy specimens from this group, under high power magnification, fields were often found directly in the line of incision in which not a single fibroblast could be seen, although macrophages were plentiful (this was nine days postoperatively). As a general rule, in the latter group of animals the reticulum was finer and sparser and there was much less collagen than was found in control animals (fig. 3). This difference appeared sufficient to explain the structural weakness and the resultant disruption of wounds which were observed.

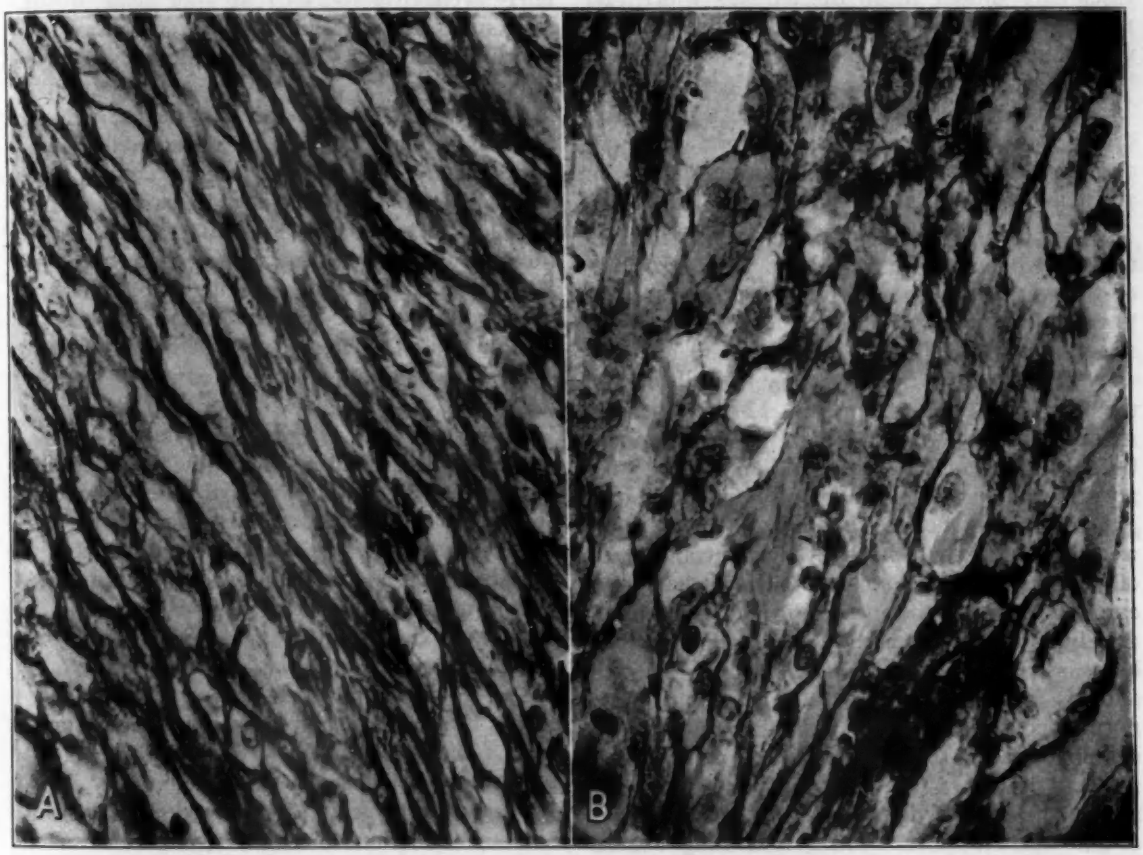

Fig. 3.—Photomicrographs (×630) of sections taken across the plane of incision of laparotomy wounds nine days postoperatively from (*A*) a normal rabbit and (*B*) a rabbit sensitized to horse serum. Both received horse serum intravenously immediately after operation. Note the sparseness of fine reticulum and the absence of collagen in (*B*), although macrophages are plentiful. This wound partially disrupted. (Stained with a combination of Bielschowsky's silver impregnation method with Hansen's modification of Van Gieson's stain for collagen.)

When biopsy specimens from this series of animals which had received foreign protein intra-

venously after operation were compared with those from a group of 19 animals which had been subjected to a similar operative procedure but which had not received foreign protein intravenously, it was observed that in the animals of the former group considerably more degenerative changes in skeletal muscle had occurred at the site of the laparotomy wound. There was waxy degeneration of many of the fibers; others exhibited necrosis and were in the process of being digested by macrophages. These changes were essentially similar in all the animals which had received either horse serum or egg albumin after operation, regardless of whether or not they had been previously sensitized to the injected protein. These changes did not appear to alter significantly the rate or quality of the healing of the wound and they were not associated, at nine days, with an acute inflammatory reaction.

Two other experiments were carried out for reasons which will be considered later. In each of these, rabbits sensitized to horse serum and to crystalline egg albumin were used. The method of sensitization and the degree of hypersensitivity were similar to those previously described. In the first of these experiments, 12 rabbits were used. Three of these were hypersensitive to horse serum and 3 to egg albumin; 6 were normal controls. Tiny loops of plain, no. 0 catgut, thoroughly washed to eliminate tubing fluid, were implanted subdermally in the ventral surface of the abdomen. (Cutaneous surfaces had been carefully shaved the preceding day.) Immediately after this procedure 10 cc. of 35 per cent horse serum was given intravenously to the 3 animals sensitized to horse serum and to 3 normal controls. The 3 animals sensitized to egg albumin and the remaining 3 normal controls received 10 cc. of 0.35 per cent solution of egg albumin. Two of the 6 sensitized animals died of anaphylactic shock. In the remaining 4 there was no significant difference in the reaction to implanted catgut at twelve, twenty-four, forty-eight or sixty hours. In the second experiment a different sort of inflammatory agent was used, the undiluted tubing fluid from boilable catgut. Tubing fluid of boilable catgut is essentially similar in composition regardless of the type or brand of catgut selected. It consists, in major part, of homologs of benzene, such as toluene or xylene. It has been recently demonstrated by Jenkins and Dunham [6] that this substance provokes a severe degree of inflammation on contact with tissues. Tubing fluid of boilable catgut in 0.1 cc. amounts was injected intradermally into the ventral surface of the abdomen in 6 sensitized and 6 normal animals, which were then given an intravenous injection of horse serum or egg albumin in the same manner as described previously. Four of the 6 hypersensitive rabbits survived the injection of specific antigen. At twenty-four, forty-eight and sixty hours a significant difference was observed between the reactions of the sensitized animals and those of the control animals. In the control animals a fairly well circumscribed area of acute inflammation developed which on the average measured approximately 1.5 cm. in diameter. A small area of central necrosis was present in most instances. In the sensitized animals, however, the area of inflammation was less well circumscribed and 50 to 100 per cent larger. Central necrosis was more extensive and less well defined. These observations demonstrate the potency of tubing fluid as an inflammatory agent and show that inflammation produced by such a substance will, under proper circumstances, provoke an Auer reaction, whereas catgut per se is relatively innocuous in this respect.

6. Jenkins, H. P., and Dunham, C. L.: Irritant Properties of Tubing Fluids as a Factor in the Tissue Reactions Observed with Surgical Gut (Catgut), Ann. Surg. **118**:288, 1943.

COMMENT

It has been demonstrated in the preceding section that the healing of laparotomy wounds is profoundly altered in rabbits previously sensitized in which specific antigen is reinjected postoperatively. In normal as well as in sensitized control animals which receive nonspecific foreign protein, laparotomy wounds heal without significant untoward reactions. In an interpretation of these observations, the most obvious explanation is that a local anaphylactic reaction plays a predominant part. With this, however, there are other possibilities to be considered.

Local Anaphylactic Reaction.—Auer considered that local autoinoculation of the sensitized animal was accomplished by the passage of specific antigen into the inflammatory lesion as a complement of the edematous fluid which accumulated there and that in the case of an operative wound "the amount of foreign protein acting locally would be increased by the oozing of blood, serum, plasma and lymph into the wound from the severed blood and lymphatic capillary channels, all of which contain the antigen." From more recent studies concerning the localizing action of inflammatory lesions,[7] an additional

7. Burrows, H.: Some Factors in the Localization of Disease in the Body, New York, William Wood & Co., 1932. Fox, J. P.: The Localization and Concentration of Blood-Borne Antibodies and Colloidial Dye in Areas of Inflammation of Various Ages, J. Immunol. **31**:293, 1936. Rigdon, R. H.: Capillary

(Footnote continued on next page)

mechanism to explain local autoinoculation is suggested. It has been shown that acute inflammatory processes localize and concentrate such vital dyes as trypan blue, Chicago blue and Evans blue when given intravenously and that protein substances too, e. g., hemolysins, agglutinins and antitoxins, may be localized under such conditions. It appears from this that antigen and antibody, or products thereof, may be actively concentrated in areas of inflammation, in addition to any passive accumulation that may occur. Such local accumulation would provoke allergic inflammation of the type and degree illustrated by the Arthus reaction.

Catgut per se does not provide an adequate stimulus for local accumulation of antigen and antibody, as has been shown. This fact is in keeping with the observation that in sensitized rabbits into which specific antigen was reinjected postoperatively, the reaction to catgut sutures in the abdominal wounds was not significantly altered. It will be recalled that all catgut used was of the nonboilable variety and had been carefully washed free of tubing fluid in several changes of warm sterile saline solution before being used in animals. The effects of tubing fluid have been described, and the facts demonstrated that tubing fluid of boilable catgut is in itself a potent inflammatory agent and that inflammatory lesions produced by that substance can elicit an Auer reaction.

Direct or Indirect Effects of General Anaphylaxis.—The profound effects obtained from the introduction of large amounts of specific antigen into sensitized rabbits is illustrated by the fact that in the experiments described 16 of 37 animals so treated died of anaphylactic shock. In the survivors, effects of impaired circulation, toxic substances in the blood or metabolic disturbances, such as might result from extensive necrosis of the liver, described by Hartley and Lushbaugh,[8] may well have influenced the healing wound adversely. It is to be noted, however, that except in 2 or 3 instances these animals appeared to have recovered from any ill effects of this treatment within twenty-four hours or less.

Local Formation of Antibodies.—It has been observed that the degree of inflammation present at nine days in healing wounds of sensitized animals into which specific antigen has been reinjected does not differ appreciably from that of control animals in which healing of the wounds is satisfactory. This fact would tend to discredit local allergic inflammation, of the type described by Auer, as the principal mechanism responsible for the decreased tensile strength exhibited by the wounds of specifically sensitized animals after reinjections. The major abnormality in these wounds, and one which appeared adequate to explain their lack of tensile strength, was the relative sparsity of fibroblasts and collagen, as has been illustrated in figure 3. Since the number of potential fibroblasts in these wounds was within normal limits, it was concluded that a failure of normal maturation of macrophages into fibroblasts had occurred. To explain this phenomenon, two possible mechanisms were considered: (1) Some toxic substance and/or abnormal catabolic products had caused injury to macrophages so that their development was altered, or (2) these macrophages were in the process of forming antibodies and, as a result of this internal stimulus, failed to develop into fibroblasts. That macrophages can form antibodies at a site of local inflammation has been well demonstrated by Cannon and Sullivan [9] and by Hartley.[10] In an area of inflammation in which antigen is introduced, there seems little doubt that the macrophages present would engage in the process of forming antibodies. It may be that macrophages retain their status as macrophages so long as they are called on to perform duties which they only, as progenitors of fibroblasts, are able to perform. When they have become fibroblasts, their ability to phagocytose and to produce antibodies is markedly diminished or lost altogether. Apparently the

Permeability in Areas of Inflammation Produced by Xylene, Arch. Surg. **41**:101 (July) 1940. Rigdon, R. H.: Localization of Staphylococci in Areas of Inflammation Produced by Xylene, ibid. **41**:879 (Oct.) 1940. Rigdon, R. H.: Observations on Capillary Permeability in Areas of Inflammation Produced by Staphylococci, Surgery **9**:436, 1941. Rigdon, R. H., and Haynes, A.: Observations on Capillary Permeability and Inflammation in the Skin of Sensitized Rabbits, J. Lab. & Clin. Med. **27**:598, 1942. Rigdon, R. H.; Ewing, F., and Tate, A.: Effects of Infra-Red Irradiation on the Tissues of the Rabbit, Am. J. Path. **19**:517, 1943; Rigdon, R. H.: Localization and Concentration of Staphylococcus Antitoxin in Areas of Rabbit's Skin Treated with Ultraviolet Irradiation, Am. J. Roentgenol. **50**:101, 1943. Rigdon, R. H., and Curl, H.: Effect of Roentgen Irradiation on Capillary Permeability and Inflammation in the Skin of a Rabbit, ibid. **49**:250, 1943. Rigdon, R. H.: Localization and Concentration of Staphylococcus Antitoxin in Areas of Rabbit's Skin, J. Lab. & Clin. Med. **27**:37, 1941. Menkin, V.: Dynamics of Inflammation: An Inquiry into the Mechanism of Infectious Processes, New York, The Macmillan Company, 1940.

8. Hartley, G., Jr., and Lushbaugh, C. L.: Experimental Allergic Focal Necrosis of the Liver, Am. J. Path. **18**:323, 1942.

9. Cannon, P. R., and Sullivan, F. L.: Local Formation of Antibody by the Skin, Proc. Soc. Exper. Biol. & Med. **29**:517, 1932.

10. Hartley, G., Jr.: The Local Formation of Antivaccinal Antibodies by the Skin, J. Infect. Dis. **66**:44, 1940.

incentive to remain macrophages and form antibodies is stronger than the incentive to mature into fibroblasts and form collagen as a process of the healing of wounds. The probable course of events in wounds which heal under such conditions is illustrated in figure 4.[11]

It may be recalled that in all animals which received foreign protein intravenously after operation, regardless of specific sensitivity, certain degenerative changes in the tissues of the wounds were more pronounced than in control animals

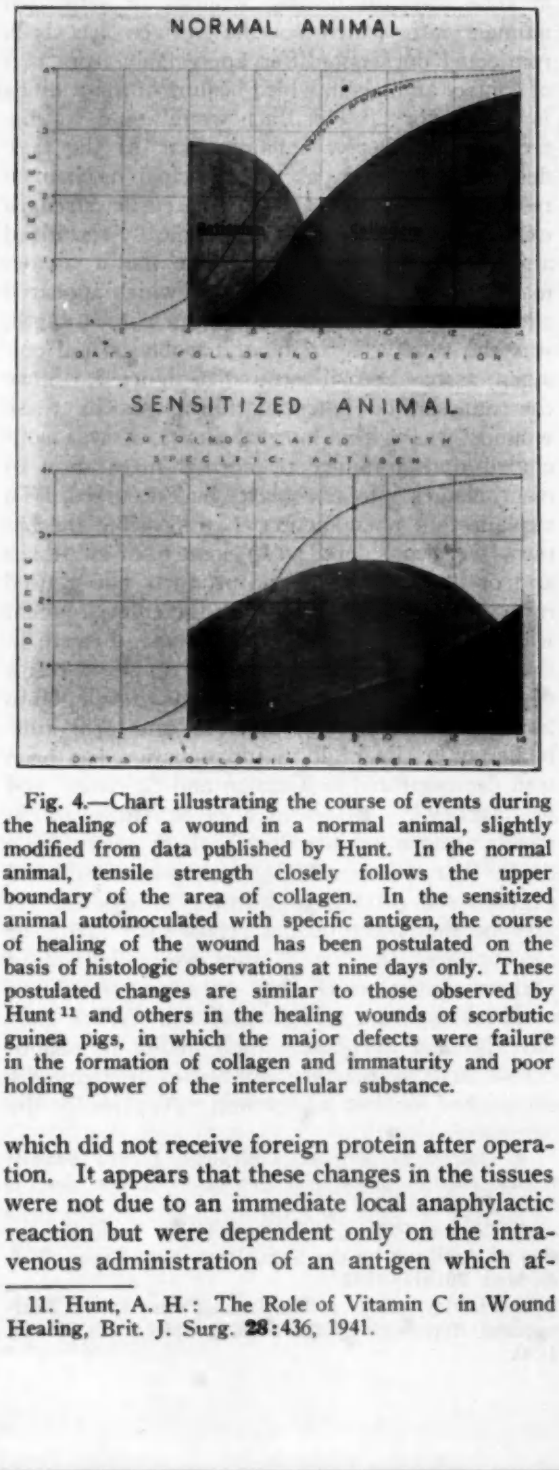

Fig. 4.—Chart illustrating the course of events during the healing of a wound in a normal animal, slightly modified from data published by Hunt. In the normal animal, tensile strength closely follows the upper boundary of the area of collagen. In the sensitized animal autoinoculated with specific antigen, the course of healing of the wound has been postulated on the basis of histologic observations at nine days only. These postulated changes are similar to those observed by Hunt [11] and others in the healing wounds of scorbutic guinea pigs, in which the major defects were failure in the formation of collagen and immaturity and poor holding power of the intercellular substance.

which did not receive foreign protein after operation. It appears that these changes in the tissues were not due to an immediate local anaphylactic reaction but were dependent only on the intravenous administration of an antigen which afforded, through the mechanism of local autoinoculation, the condition necessary for the formation of antibodies locally within the wound.

A possible explanation for the differences between the healing processes of sensitized animals which received specific antigen and those of animals which received nonspecific antigen rests on the fact that in the former group the animals had been previously prepared with specific antigen and were thus able to form antibodies more efficiently and at a faster rate. This phenomenon of specific anamnesis is discussed in a recent work by Cannon.[12] Such a reaction provides for a considerably greater stimulus for the production of antibodies in specifically sensitized animals and would afford a greater stimulus for the macrophages in the healing wounds of these animals to remain macrophages, rather than to mature into fibroblasts.

The clinical significance of this mechanism is probably not great; however, instances in which all of the factors necessary to bring about this mechanism are present certainly occur, and in such instances a local allergic reaction of the type described may act to produce delayed fibroplasia and disruption of the wound.

As a precautionary measure against such a reaction it is suggested that when abdominal operations are performed in the presence of chronic abdominal inflammatory lesions these lesions should be carefully protected from any trauma or, if their removal is desired, they should be "isolated" initially by means of clamps or ligatures. Such abdominal wounds should be thoroughly reenforced with nonabsorbable sutures and abdominal binders in order that the wounds may retain their initial "mechanical" strength for a longer period than is ordinarily required.

SUMMARY AND CONCLUSIONS

Local allergic reaction at the site of a surgical wound will delay healing and encourage disruption.

The mechanism of such delayed healing appears to rest in a failure of the maturation of macrophages, with resultant failure in the production of the reticulum and collagen.

There are several possible explanations for this mechanism, which is of clinical significance in certain cases in producing disruption of wounds.

Prof. Paul R. Cannon, of the Department of Pathology, gave valuable suggestions.

950 East Fifty-Ninth Street.

11. Hunt, A. H.: The Role of Vitamin C in Wound Healing, Brit. J. Surg. **28**:436, 1941.

12. Cannon, P. R.: Antibody Production and the Anamnestic Reaction, J. Lab. & Clin. Med. **28**:127, 1942.

PROGRESSIVE GANGRENE IN AN OPERATIVE WOUND

DONALD W. LEONARD, M.D.

CAMBRIDGE, N. Y.

The object of this article is to report a case of extensive destruction of the skin and the subcutaneous tissue in an operative wound closed after a routine removal of a gangrenous appendix and to discuss the observations already reported in medical literature regarding this rare but definite clinical entity. The case to be described is from the Mary McClellan Hospital, service of Dr. Denver M. Vickers, and it is through Dr. Vickers' cooperation that this report is made possible. All surgical procedures were carried out under his direction or by him personally, and his recollection of a similar account in the literature led to the finding of the first useful understanding of the problem.

Necrosis of a wound as a postoperative complication has been described enough in medical periodicals to be established as a definite entity with a definite mode of progression. Its appearance, as will be shown, is an indication for surgical intervention, as urgent as that for the operation which preceded it. Satisfactory treatment has been shown to depend on the recognition of this fact, inasmuch as the complication has never been known to yield to the measures ordinarily applied to the simple infections of wounds which it at first resembles. Failure to be aware of the possibility that such a postoperative situation can arise and consequent failure to profit by the experience of others may permit the ulceration to reach a considerable size.

In the course of the futile orthodox treatment of our patient a search of the literature was made without a clear idea of just what to look for. An article by Cullen published in 1924 was found to contain a complete description of a case with an excellent colored drawing, which might have served equally well as an illustration of our problem. This apparently was the second record of a case and began the chronologic list of reports later discovered, each article usually containing a description of a single case. The vital importance of these references in the satisfactory treatment of our patient and the complete absence of information in most textbooks seem to justify the publication of further observations from our experience and a review of the conclusions set forth by other surgeons.

From the Mary McClellan Hospital.

CLINICAL OBSERVATIONS

The complication under discussion begins characteristically a week or more after operation and at a time when the sutures may have been removed from an apparently well healed incision. The first sign of trouble is a puffiness of the wound, giving evidence of a subcutaneous accumulation of fluid, as it does in many other instances when there is a collection of serum or pus resulting from exudate in tissue or infection. With this sign the most conservative treatment calls for a separation of the firmly united edges of skin at some point to allow the escape of the fluid. A small cavity is left, as is to be expected, but the whole situation to this point does not suggest anything too unusual. However, when a thinning of the entire scar and a separation of the edges by necrosis occur, it becomes obvious that a serious complication has developed, unchecked by the usually adequate drainage.

At this point, according to the published reports and to our own observations, the seriousness of the problem should be recognized and radical excision of the entire ulcerating area done. No writer has yet escaped this conclusion, but it is also true that in practically every instance in which this gangrenous ulceration has appeared it has been so unexpected that it has progressed far beyond this stage before the attending surgeon has felt justified in entering the healthy surrounding tissue with a knife unavoidably contaminated by this grossly septic lesion. Delay has caused further spread in all directions, faster longitudinally but always characterized by advancing necrosis of cutaneous margins, which become blackened into a drying slough floating on a gangrenous mass of subcutaneous fat honeycombed with purulent fluid and attached to surrounding skin, which shows for a variable distance a purple induration that seems to be the location of whatever pain the patient experiences. With all of this, in spite of wide extension, there is almost no systemic reaction other than that of the exhausting anxiety due to the inexorable advance of the process, which the patient can see as clearly as does his physician.

Source of Ulceration	Patient Age	Patient Sex	Date of Operation	Result	Author
Appendectomy	50	M	9/28/22	Recovered	Cullen, 1924
Appendectomy	53	M	12/23/24	Recovered	Alexander, 1926
Appendectomy	64	M	12/18/25	Recovered	Brewer and Meleney, 1926
Appendectomy	39	M	11/24/26	Recovered	Gillespie, 1928
Appendectomy	34	M	5/24/27	Recovered	Cole and Heideman, 1929
Appendectomy	..	M	2/../27	Recovered	Lynn, 1931
Appendectomy	62	M	6/../29	Recovered	Lynn, 1931
Appendectomy	52	M	10/16/29	Died	Liedberg, 1935
Appendectomy	32	M	10/20/30	Recovered	Baker and Terry, 1932
Appendectomy	54	M	1930	Recovered	Hellstrom, 1930
Appendectomy	35	M	1/../31	Recovered	Meleney, 1931
Appendectomy	45	M	6/17/31	Recovered	Horsley, 1932
Appendectomy	62	F	8/11/31	Recovered	Meleney, 1933
Appendectomy	62	M	8/15/31	Recovered	Scotson, 1933
Appendectomy	57	F	2/ 5/35	Recovered	Willard, 1936
Appendectomy	46	M	12/../39	Died	Callam and Duff, 1941
Appendectomy	49	F	11/../34	Recovered	Blaxland, 1935
Appendectomy	52	M	.....	Recovered	Ballin (Freeman, 1930)
Appendectomy	..	M	.....	Recovered	Shipley, 1928
Appendectomy	62	F	.....	Died	Vohnout, 1933
Appendectomy	45	M	.....	Recovered	Poerschke, 1933
Appendectomy	32	M	.....	Recovered	Brewer and Meleney, 1926
Appendectomy	48	M	.....	Recovered	Moschowitz (Brewer, 1926)
Appendectomy	..	F	.....	Recovered	Meleney, 1935
Appendectomy	38	M	.....	Recovered	Mayeda, 1926
Appendectomy	38	M	.....	.....	Gordon, 1928
Appendectomy	70	M	.....	Died	Mitchell (Lynn, 1931)
Appendectomy	32	M	.....	Recovered	Terry (Lynn, 1931)
Appendectomy	37	M	.....	.....	Clinton, 1926
Appendectomy	35	F	.....	.....	Porter, 1926
Appendectomy	..	..	.....	.....	Warfield, 1927
Appendectomy	62	M	.....	Died	Carol, 1932
Thoracotomy	62	M	9/../19	Died	Blaxland, 1935
Thoracotomy	62	M	6/20/30	Recovered	Patterson, 1932
Thoracotomy	36	M	10/22/30	Died	Poate, 1930
Thoracotomy	44	F	5/17/33	Recovered	Santy, 1936
Thoracotomy	54	M	1933	Recovered	Callam and Duff, 1941
Thoracotomy	44	M	2/13/34	Recovered	Stewart-Wallace, 1935
Thoracotomy	60	M	.....	Recovered	Taxernier (Tixier and Pollosson, 1936)
Thoracotomy	54	M	.....	Recovered	Ballin (Freeman, 1930)
Thoracotomy	48	M	.....	Died	Brunsting, 1930
Thoracotomy	64	M	.....	Recovered	Christopher, 1924
Ruptured peptic ulcer	57	M	10/30/32	Recovered	Meleney, 1933
Ruptured peptic ulcer	57	M	6/ 5/33	Recovered	Scotson, 1933
Ruptured peptic ulcer	44	M	.....	Recovered	Cox, 1936
Axillary abscess	25	F	2/ 6/31	Recovered	Holman, 1935
Axillary abscess	20	F	9/ 1/33	Recovered	Holman, 1935
Axillary abscess	25	M	3/30/34	Recovered	Hirshfeld, 1939
Inguinal abscess	..	M	10/../25	Died	Meleney, 1935
Inguinal abscess	8	M	1930	Recovered	Ballin and Morse, 1931
Inguinal abscess	33	M	2/21/31	Recovered	Horsley, 1929
Abdominal wall abscess	55	M	5/30/08	Recovered	Luckett, 1909
Abdominal wall abscess	..	M	1/ 5/27	Recovered	Shipley, 1928
Hepatic abscess	63	F	.....	.....	Brewer and Meleney, 1926
Hepatic abscess	..	..	.....	.....	Tavernier (Tixier and Pollosson, 1936)
Pelvic abscess	..	F	10/../27	Died	Meleney, 1935
Pelvic abscess	46	F	.....	.....	Borelli, 1924
Hysterectomy	42	F	.....	Recovered	Meleney, 1935
Hysterectomy	..	F	.....	Recovered	Meleney, 1935
Cecostomy	63	F	12/../31	Recovered	Meleney, 1933
Cecostomy	..	..	.....	.....	Delmas, 1937
Gastroenterostomy	45	M	.....	Recovered	Tixier and Pollosson, 1936
Gastric resection	21	M	.....	Recovered	Constantinescu, 1938
Cholecystectomy	39	F	3/27/29	Died	Freeman, 1930
Peritoneal abscess	..	F	.....	Recovered	Meleney, 1935
Rectal cancer	54	F	.....	Died	Pergola and Rosenfeld, 1938
Ventral hernia	64	F	1925	Recovered	Ballin and Morse, 1931
Mammary abscess	35	F	6/16/26	Recovered	Probstein and Seelig, 1928
Intussusception	67	M	12/14/27	Recovered	Horsley, 1929
Pilonidal sinus	28	M	9/../37	Recovered	Hirshfeld, 1939
Epididymal abscess	18	M	.....	Recovered	Ballin (Freeman, 1930)
Pelvic exploration	42	F	2/ 6/31	Died	Holman, 1935
Pustule on leg	48	M	7/../34	.....	Holman, 1935

Summary of Cases Reported—Continued

Source of Ulceration	Patient: Age	Patient: Sex	Date of Operation	Result	Author
Appendectomy *	45	M	.....	Recovered	Stich (Liedberg, 1936)
Appendectomy *	40	M	.....	.....	Grauhahn (Liedberg, 1936)
Appendectomy *	50	M	.....	Recovered	Brown (Liedberg, 1936)
Appendectomy *	11	F	.....	Recovered	Hohmeier (Jaeger, 1938)
Appendectomy *	56	M	.....	Died	Kappis, 1932
Appendectomy *	67	M	.....	Recovered	Syme and Bryce, 1936
Appendectomy *	49	M	.....	Recovered	Coakley and Klein, 1936
Appendectomy *	58	M	.....	Recovered	Philipowicz, 1936
Appendectomy *	50	M	.....	Recovered	Syme, 1936
Appendectomy *	45	..	.....	Recovered	Carroll, 1938
Appendectomy *	44	M	.....	Died	Sussi, 1937
Appendectomy *	48	M	.....	Recovered	Wolanski, 1939
Appendectomy	60	F	4/26/39	Died	Dodd, Heekes and Geiser, 1941
Appendectomy	69	F	7/14/42	Died	Davison, Sarnat and Lampert, 1944
Thoracotomy *	58	F	.....	Recovered	Hicken, 1935
Thoracotomy *	47	F	.....	Recovered	Brandberg, 1937
Ruptured peptic ulcer *	43	M	.....	Recovered	Duemling and Elston (Liedberg, 1936)
Ruptured peptic ulcer *	57	M	.....	Recovered	Nightingale, 1934
Ruptured peptic ulcer *	77	M	.....	Died	Waschulewski, 1939
Inguinal abscess *	4	M	.....	Recovered	Ballin and Morse, 1931
Inguinal abscess *	74	F	.....	Died	Wachs, 1937
Abdominal wall abscess *	52	M	.....	Died	Krecke (Kappis, 1932)
Abdominal wall abscess *	36	M	.....	Recovered	Cudnovskaja (Kappis, 1932)
Subphrenic abscess *	42	M	.....	Died	Wachs, 1937
Umbilical abscess *	24	F	.....	Died	Wachs, 1937
Pelvic abscess *	29	F	.....	Died	Schlink and Thomson, 1935
Intestinal obstruction	67	M	.....	Recovered	Dodd, Heekes and Geiser, 1941
Cholecystectomy *	44	F	.....	Recovered	Kueppers, 1935
Cholecystectomy *	67	M	.....	Recovered	Wakeley and Willway, 1937
Cholecystectomy *	58	F	.....	Recovered	Tamman (Liedberg, 1936)
Herniotomy *	64	F	.....	Recovered	Tennant (Freeman, 1930)
Herniotomy *	65	M	.....	Died	Stohr and Niederland, 1935
Mammary abscess *	32	F	.....	Recovered	Liedberg, 1936
Prostatectomy	60	M	7/10/39	Died	Dodd, Heekes and Geiser, 1941
Sympathectomy on thigh *	50	M	.....	Recovered	Kappis, 1932
Abscess of tibia *	29	F	.....	Died	Diebold, 1934
Pustule on leg *	72	M	.....	Died	Kappis, 1932
Hand infection *	26	M	.....	Recovered	Wachs, 1937
Varicose ulcer *	66	F	.....	Recovered	Wachs, 1937

* Foreign references cited by Dodd, Heekes and Geiser, 1941, and included in their bibliography.

PREVIOUS REPORTS

Accumulated experience will not give the surgeon much practical aid in reaching a decision about the cause of this complication, which spreads with such dramatic speed while he watches it. Reports of cultures are confusing, because many of the organisms isolated are of the usual varieties and it is impossible to understand why this lesion differs from others from which the same organisms are isolated. An amebic infection, apparently proved to be present in the cases of Cole and Heideman, or the synergistic bacterial combination discussed by Meleney in 1931 may appear to be attractive possibilities, but whether any of the varied technics employed or the chemicals recommended have any special virtue has not been determined because of the lack of material. In reading one is certainly confronted with an enumeration of the standard methods of treatment for infection of wounds that have definitely failed until excision was done. The successful healing of the lesions discussed in the literature with the application of certain theoretically correct chemicals after excision appears to have made persons enthusiastic who have ignored the possibility that the ulceration may heal spontaneously after the gangrenous advance has been stopped. It can also be correctly assumed that the failure of any chemical agent to stop the advance of the gangrenous process does not indicate that it is necessarily ineffectual against the unknown etiologic agent. It may rightly be assumed that it merely fails to reach the advancing margin until after the latter is uncovered by excision.

Thus a reference to literature creates a confusion which, by contrast, makes the simplicity of excision more evident. All the cases together furnish indirectly the proof that excision is urgently needed as soon as these characteristic

developments appear in a postoperative wound. The conditions for which the operations were done in the recorded cases of postoperative gangrenous ulceration are widely varied, but each author has had the same urge to share the experience and the lesson he learned from it. A study of the details in these reports justifies some question as to whether or not all of the lesions conform to the classic picture, but for a statistical study all of the 112 examples from the literature may be listed in a table, which is an expansion of similar summaries presented by Stewart-Wallace and Holman in 1935 and Dodd, Heekes and Geiser in 1941 (table).

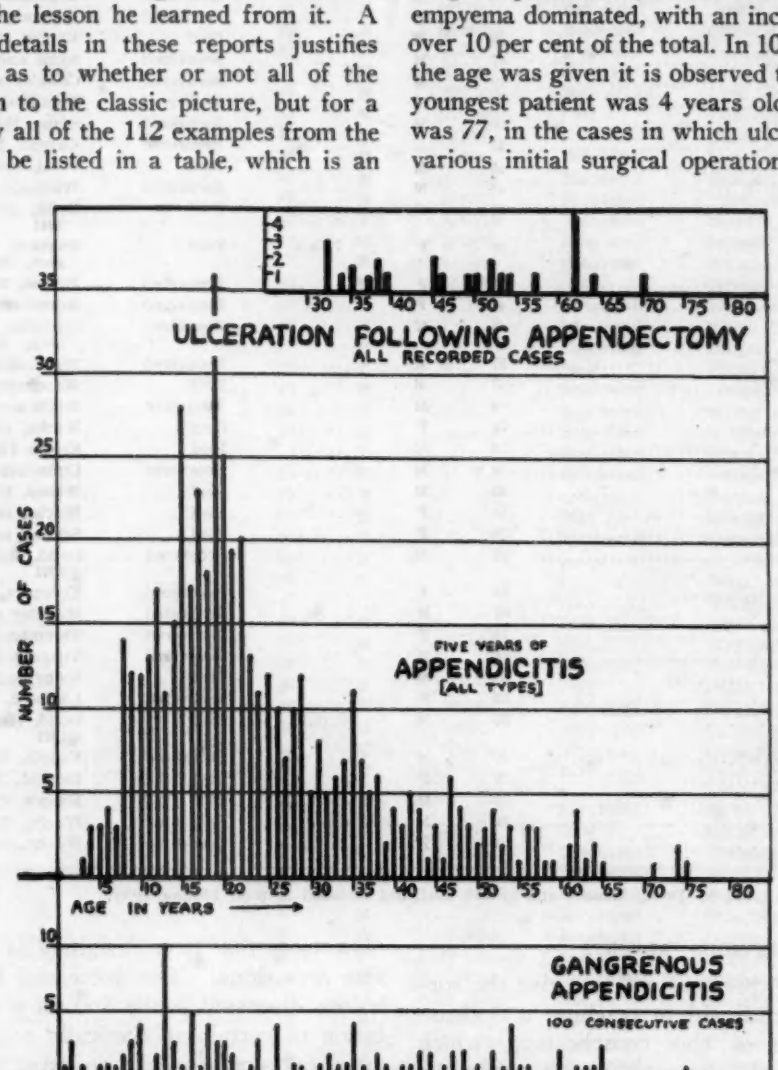

Fig. 1.—Comparison of the age distribution of cases of simple appendicitis, gangrenous appendicitis and ulceration following appendectomy. The last group appears well beyond the peaks of the curves for the other two and gives basis for the inference that the development of postoperative gangrenous ulceration in the wound depends on factors other than those related to the appendicitis itself.

From the information in the summary of the cases in the literature it is possible to make several interesting generalizations about the gangrenous ulceration, although incomplete data in many cases make it necessary to use only a part of the total number. Thus it is observed that 108 reports stated the sex of the patient but that in 68 per cent of these it was male. By a similar simple calculation it is discovered that in nearly 42 per cent of the cases the gangrenous ulceration followed operation for appendicitis and that in the rest it occurred after 31 different surgical procedures, of which thoracotomy for empyema dominated, with an incidence of a little over 10 per cent of the total. In 101 cases in which the age was given it is observed that whereas the youngest patient was 4 years old and the oldest was 77, in the cases in which ulceration followed various initial surgical operations as well as in the smaller group in which it followed appendectomy, there was a rather uniform distribution of patients between the ages of 30 and 65 years.

Inasmuch as these figures indicate that postoperative gangrenous ulceration seems to follow appendectomy with greatest frequency, it is interesting to speculate about a possible relationship and to compare the age distribution, for one thing, with that for appendicitis (fig. 1). In The Mary McClellan Hospital for a five year period it will be noted that the age of greatest

incidence of appendicitis of all types is definitely between 10 and 30 years. This conclusion is reached from inspection of figures from this hospital, but it is equally true of other tabulations of the same kind and may be accepted as a universal fact. The ulceration under consideration seems, therefore, to be related to other factors than those of appendicitis itself or the chance infection of the postoperative wound. However, if a tabulation of the age incidence of gangrenous or perforated appendicitis and of ulceration following appendectomy is made (fig. 1), a wider distribution through the years is shown for the former and a relatively higher percentage of older patients appears to have had the latter, more severe complication. This suggests that some individual tissue susceptibility may appear in the later years of life after a septic surgical operation.

ulceration instead of merely a temporary delay of healing until the tissues immunize themselves against septic discharges. If it can be assumed that certain persons in the later years of life lack the power to produce immunity of the tissues and that their lack is more pronounced in the winter months, a warning of potential difficulty may be accepted, especially if this combination occurs in a male patient. The recognition of the possibility may lead to a more prompt adoption of radical treatment. The argument that the condition is rare does not obviate the tragic reality of the distress when the exceptional case appears.

To draw conclusions from a relatively small series may be a questionable procedure. No other method presents itself because, even though many authors have remarked that other cases have been observed, this supposed larger number of unrecorded cases cannot be used for tabulation.

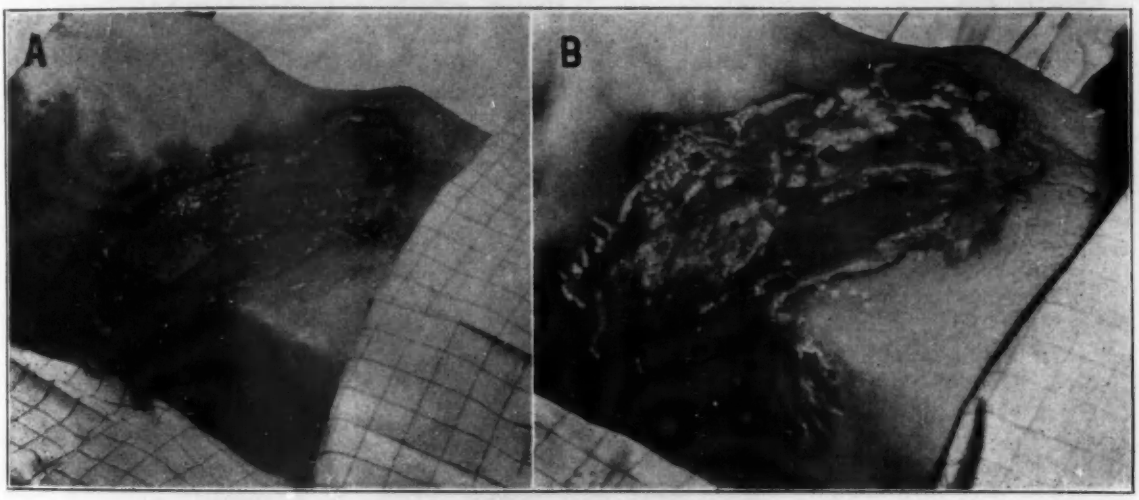

Fig. 2.—*A*, photograph of necrosis of an operative wound sixty-two days after operation and eight days after first excision of the necrotic margins with a high frequency cutting current. At the time of the excision short strokes were made at right angles to the margin and extending into the surrounding red induration, which was not removed. In the eight days following the first excision further necrosis appeared except along most of the lower margin and in two places on the upper margin. A second excision was done on the day of this photograph. *B*, photograph of the ulcerated area seventy-two days after the operation and ten days after the last excision. During the interval sulfathiazole powder was dusted on the granulating area every other day. It can be seen that active advance was stopped except at three points on the upper margin, which appear black with additional necrosis. Local excision at these three locations was done on the day of this photograph.

Further analysis of the cases in the literature in which the month of the operation was stated demonstrates that 66 per cent of the complications followed operations done in "winter months," from September to February, inclusive. A similar consideration of the cases in which gangrenous ulceration followed appendectomy leads to the fact that 69 per cent of these operations were done in the same winter months.

These observations of age incidence and seasonal distribution furnish material for a partial explanation of the situation which on certain occasions results in rapid gangrenous

TREATMENT

To the list of cases in the literature is now added 1 more. Our patient was a man of 56 who was operated on for a gangrenous appendix on Jan. 24, 1943. The case therefore conforms to the pattern for potential trouble in regard to age, sex and season. This cannot be assumed to be the only case of its kind in the last few years. It can, however, be considered to be the only available instance of the complication that illustrates the failure of some of the sulfonamide

drugs and the success of repeated conservative excisions with the electrosurgical unit in contrast to the massive excisions previously advocated (figs. 2 and 3). At the time when treatment by excision was finally undertaken, the usual local remedies, including drainage, diluted solution of sodium hypochlorite U. S. P., sulfanilamide, hydrogen peroxide, sodium perborate, ultraviolet radiation and zinc peroxide, had been tried without even a momentary arrest of the spread of the ulceration. Sulfanilamide was unfortunately the only representative of the sulfonamide compounds that was tried locally before excision of the margins. Reliance was placed on this drug because of erroneous faith in the importance of a culture from the wound. However, while this was being used locally the patient was receiving sulfathiazole by mouth at the moderate rate of 1 Gm. every four hours. If it is assumed that this dose gave sufficient concentration in the blood stream and that the advance of the process was not thereby stopped, it will be logical to assume that the circulating blood had been cut off before it reached the active margin which was undergoing necrosis and that the concentration was not effective in the protection of the tissue with a good blood supply which was later to become involved. To explain the failure of this treatment with these conclusions would imply that the gangrene resulted from bacterial action. This has not by any means been proved. The effect of higher concentrations of one of the

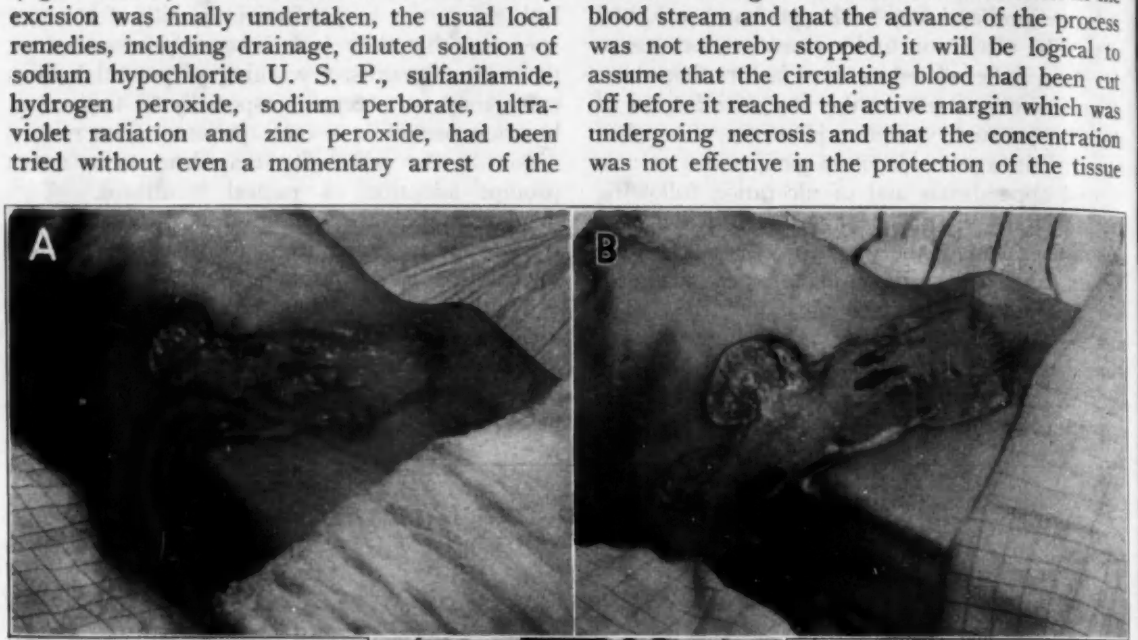

Fig. 3.—*A*, photograph of the ulcerated area eighty days after the operation and eight days after the last excision. Stubborn advance of necrosis continued at two points in spite of the last partial removal of the edge. Lighter patches through the upper half of the lesion now show clearly the extent of spontaneous growth of epithelium. The entire area is obviously smaller and the patient is free from symptoms. Another local excision was done. *B*, photograph of the lesion on the abdominal wall eighty-nine days after the operation and nine days after the last local excision. All activity at the margins has been eliminated, and the spread of the lighter area shows that nearly two thirds of the ulcerative bed has covered itself with new epithelium. At this time the use of sulfathiazole powder was discontinued and the growth of the remaining granulation tissue controlled by silver nitrate. *C*, photograph of the ulcerated area nearly completely healed, one hundred and nineteen days after the operation. Uncovered granulation tissue still shows in the suprapubic region and in a small spot above the crest of the ileum on the right side. The entire lesion has contracted to at least half its former width but gives the patient no disability. He is able to stand erect and has gained strength rapidly, with an actual increase in weight.

sulfonamide drugs should undoubtedly be determined. It is our opinion, however, that the victim of this type of ulceration deserves the more certain arrest of further expansion which surgical measures provide. Investigation in regard to the best way to accomplish this will be more fruitful than trials of medical treatment.

The first record of treatment of a lesion of this type by excision was presented in 1909 by Luckett, who stated that he made up his mind to treat his patient "wholly on surgical grounds and totally ablate the ulcer by actual cauterization." He added the remark that "the extent and magnitude of this procedure can be more fully grasped when we mention that we consumed the benzine of two freshly filled Paquelin thermocauteries in a period lasting fifty-five minutes." Cullen, in his article that appeared in 1924, first attracted attention to this entity and gave an account of his final treatment with a "cautery knife used well beyond the advancing margin." Brewer and Meleney stated in 1926 that they were successful in their use of a deep barrier created by an encircling incision packed with frequent changes of gauze soaked in 0.4 per cent solution of formaldehyde. Shipley in 1928 published his account of successful excision with a red hot wire loop cautery to separate the margin from the healthy tissue and a knife to raise it from the underlying fascial layers. Lynn in 1931 advocated the use of the "cautery or electrotherm knife." Baker and Terry in 1932 used the Bovie electrosurgical unit and excised and coagulated the entire lesion. The ulceration in the case reported by Patterson in 1932 recurred after excision within the zone of redness and was later excised widely with the actual cautery. Holman in 1935 advocated excision with cautery and maggot therapy. Willard in 1936 apparently limited his technic of excision to the use of a knife. Scotson in 1933 used a trench cut out with "diathermy cautery" as a barrier, and James, another English surgeon, was successful with the same technic.

From this summary of the methods of excision it can be seen that the same surgical intention has been carried out by various appliances, which have tended to be more accurate, more hemostatic and less injurious to the surrounding tissues as electrical technics have been developed. These surgical methods have been sufficient, and their success has made the problem of causation of secondary importance, even though its solution might give the vague promise of a means of prophylaxis.

The statement from the article by Baker and Terry to the effect that they excised and coagulated the entire lesion may be referred to again to emphasize a contrary opinion. One of the most fantastic features of our case was the spontaneous epithelization of the central area while the necrosis at the margins was still rapidly spreading. It was surprising that although the entire lesion grew to cover about two thirds of the surface of the abdomen, healing in the center had so far advanced at the time of the last excision that epithelization was complete in only twenty additional days. This rapid healing was obviously due to the miraculous appearance of islands of epithelium in places where the destructive necrosis had apparently been total. For this reason it is believed that coagulation of the entire lesion at any stage might have been a serious mistake.

REPORT OF A CASE

The appearance of this unexplained type of necrosis of a postoperative wound in a case in our service has been mentioned as a reason for this review of the subject. Certain details of this case have been mentioned in the discussion of the treatment, along with an enumeration of the standard measures that apparently failed. Effective treatment was not begun until the fifty-fourth day of the complication, and it is freely admitted that at that time the condition was entirely out of control and the situation desperate. Limited excision of the active margins turned the tide, and the central areas proliferated healthy granulation tissue toward these margins. In the end, after three more partial excisions, we were convinced that less healthy tissue had been sacrificed than would have been with a massive excision. That the whole lesion seemed smaller rather than larger with each successive excision is well illustrated in photographs (figs. 2 and 3).

SUMMARY

A review of articles presenting examples of progressive necrosis of postoperative wounds has been given, and from their tabulation the following observations have been made:

1. Progressive necrosis of postoperative wounds (sometimes termed phagedenic ulceration) is a clinical entity having a definite onset, characteristic features and a predictable course.

2. It occurs more frequently in males.

3. It develops most frequently in patients between the ages of 30 and 65 years.

4. This complication usually follows surgical procedures for drainage of septic conditions during the winter months.

5. It appears most frequently after removal of a gangrenous appendix and next frequently after costal resection for empyema.

6. All reports indicate that the only successful treatment is surgical excision of the affected area.

From our observations made on the course and the treatment of this type of necrosis of postoperative wounds the following additional conclusions have been reached:

1. A rapidly advancing necrotic margin involving skin and subcutaneous fat and following the spread of a dark red cutaneous inflammation which radiates from the operative incision is the characteristic picture of this condition. It is our feeling that spontaneous healing and rapid epithelization of the central portions of the ulcer are equally characteristic. The two processes proceed simultaneously, and there is no satisfactory evidence that any antiseptics so far applied have altered either process before the margins have been removed by excision. When this has been done, the spontaneous healing is so pronounced that a simple protective dressing is probably sufficient.

2. Diagnosis may be made from the clinical picture and effective treatment instituted without confusing and controversal bacterial studies. The rare appearance of this condition reduces the importance of routine prophylaxis, and discussions should therefore stress the importance of early recognition and conservative excision.

3. Early recognition of the characteristic changes in an operative wound and prompt adoption of treatment by excision will reduce this entity to a complication of relatively minor importance, with a short period of additional disability. Failure to adopt this surgical treatment promptly will result in weeks of uncertainty, a long period of disability and a disfiguring scar.

4. Sulfathiazole given by mouth and sulfanilamide powder applied locally apparently have no effect on the progression of the gangrene before excision of the margins of the ulceration.

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REGIONAL ENTERITIS

PATHOLOGIC STUDY OF TWENTY-TWO CASES

FREDERICK M. OWENS JR., M.D.
CHICAGO

The condition known as "regional enteritis" was first established as an entity by Crohn, Ginzburg and Oppenheimer [1] in 1932. It has been variously referred to since that time as "terminal ileitis," "regional ileitis" and "regional enteritis." The last term is that most commonly accepted at the present time, for the disease is not confined to the ileum but may involve any portion of the small bowel and even the large bowel.

Crohn and his collaborators emphasized the occurrence of different stages or phases of regional enteritis, which they characterized as (1) the acute inflammatory phase, (2) the ulcerative phase, (3) the stenotic phase and (4) the phase of formation of fistulas. The first two might be referred to as acute stages and the last two as chronic. However, an important gross differential feature is the patchy or segmental involvement of the bowel. It should be emphasized that lesions of the different phases may be present in different segments and that all four types of lesions may coexist in the same bowel. Of course some of the features of regional enteritis are shared by other ulcerative diseases, especially by nonspecific ulcerative colitis. The latter differs, however, in its predilection for the colon, particularly for the descending portions of the colon. Grossly, there is relatively little similarity to specific infectious diseases which affect the intestines or to neoplastic diseases. Only occasionally a specific infectious disease, such as hyperplastic tuberculosis, resembles regional enteritis.

While little has been added to the excellent original description of the gross pathologic changes, descriptions of microscopic observations have usually been incomplete and variable. In part this may be accounted for by the small number of cases studied by any one observer.

Dr. Eleanor Humphreys gave her assistance.

From the Department of Surgery of the University of Chicago.

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1. Crohn, B. B.; Ginzburg, L., and Oppenheimer, G. D.: Regional Ileitis: A Pathologic and Clinical Entity, J. A. M. A. **99**:1323 (Oct. 15) 1932.

A careful review of microscopic material derived from 22 cases observed at the University of Chicago Clinics was undertaken. These cases provided examples of both acute and chronic stages of regional enteritis, as well as of major complications. This study has served to emphasize certain consistent microscopic features and to bring out certain differential criteria. For purposes of correlation and to avoid repetition, the microscopic observations in these cases have been summarized with particular reference to the changes occurring in the separate coats of the intestinal wall.

MATERIAL STUDIED

This survey is based on the study of multiple sections from various portions of each bowel or segment of bowel examined. The 22 cases represented a wide range in terms of acuteness or chronicity. The duration of symptoms was from eighteen weeks to thirteen years. There were 15 males and 7 females. The ages ranged from 12 years to 41 years, average 29.6 years. In 16 cases only surgically excised segments were available, but in 2 of these it was possible to examine sections of bowel removed at more than one operation. In 5 cases it was possible to compare observations on resected segments with those on remaining segments of the bowel obtained at autopsy. In 1 case only autopsy material was available.

MICROSCOPIC OBSERVATIONS

Changes in the Mucous Membranes.—The earliest phase of inflammation has been, for obvious reasons, as yet unobserved. In early acute lesions (eighteen weeks) as well as in more acute lesions which coexisted with chronic ones, ulceration was already present. As established from gross observations, ulceration is usually patchy. The more acute ulcers tend to lie primarily on the mesenteric border, but with extension of the process they may encircle the lumen or may extend for considerable distances longitudinally. However, a characteristic feature, seen even where there is extensive ulceration, is the presence of islands of intact mucosa of varying size. In the less chronic stages such

Fig. 1.—Granulation tissue floor of a superficial ulcer, showing fragmented muscularis mucosae.

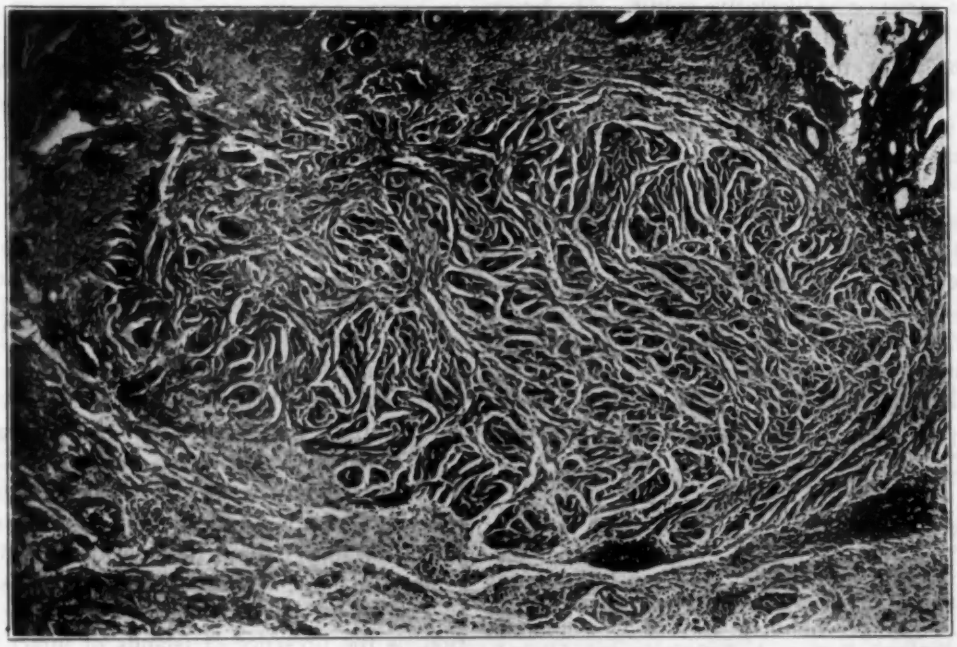

Fig. 2.—Neuromuscular hyperplasia of the muscularis mucosae.

islands often contain hypertrophied glands and project as pseudopolyps, overhanging the adjacent ulcers.

The ulcers of the acute and subacute stages, even when extensive, are often surprisingly superficial (fig. 1). They frequently are confined to the mucosa, and when they do extend through the muscularis mucosae they rarely extend as far as the main muscular coats. In general, they have floors composed of an extremely vascular granulation tissue, which contains, besides mononuclear cells of various types, moderate numbers of neutrophils and eosinophils and occasional giant cells. Not rarely thick layers of such granulation tissue lie on top of the muscularis mucosae. Productive fibroplasia in such superficial ulcers must be an important element, contributing to the subsequent stenosis. Deeper ulcers, which can be traced to sinus tracts, are not seen until the chronic stenosing phase is reached.

In the acute and subacute stages, the villi and the stroma between the glands are edematous and are densely infiltrated with inflammatory cells. Among these cells are some polymorphonuclear neutrophils and eosinophils, but the predominant cells are mononuclear cells.

In the more chronic stages the glands lose their hyperplastic features and eventually atrophy. Such glands are widely separated by a more fibrotic stroma, which still, however, may present evidence of some edema. The hypertrophic villi of the earlier stages tend also to disappear. In contrast to most intestinal lesions terminating in mucosal atrophy, however, the actual thickness of the mucous membrane is not decreased and may even be considerably increased. In fact, both the fibrosis and the edema tend to thicken it, another feature which contributes to stenosis.

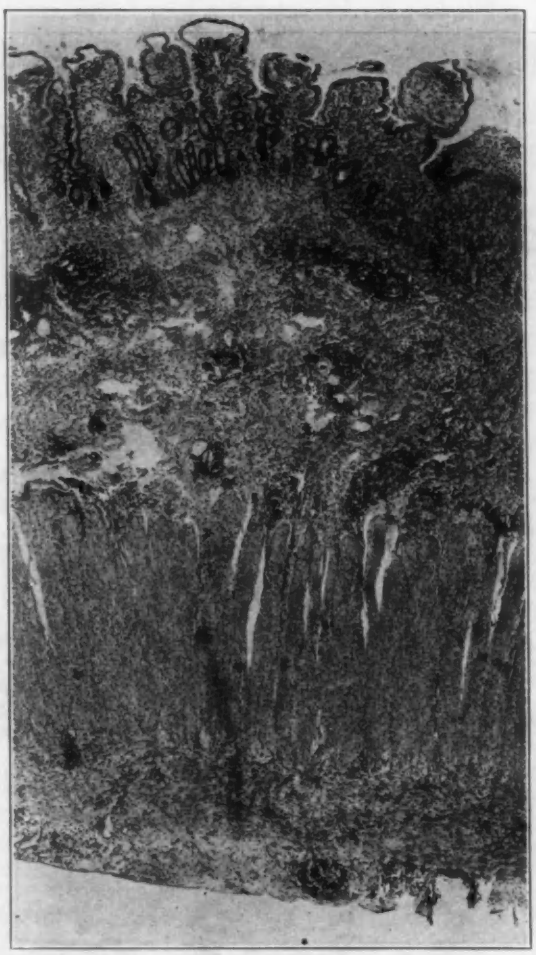

Fig. 3.—Section of the wall of the ileum, showing infiltration of the mucosa and submucosa by granulation tissue and fibrous tissue. Prominence of the ganglion cells of Auerbach's plexus is evident.

The Muscularis Mucosae.—Obviously this coat is destroyed by the deeper ulcerative lesions,

both acute and chronic. However, the extent of destruction is rarely great. A striking feature, evident fairly early and marked in the chronic phase, is proliferative thickening of this muscular coat. It is possible that this is of the nature of a neuromuscular hyperplasia, analogous to that seen in so-called "neurogenic" appendicitis. There is an increase in numbers of smooth muscle cells, as well as a gross distortion of their normal pattern (fig. 2). Such thick disarranged muscular layers are seen both in the floors of superficial mucosal ulcers and beneath the islands of mucous membrane. They are not seen at any distance from the regions of major involvement. Single and grouped ganglion cells of Meissner's plexus may be found within or on either border of the distorted muscularis mucosae.

Fig. 4.—Serosal tuberculoid granuloma containing giant cells.

The Submucosa.—The submucosal layer, in contrast to the outer coats, shares equally with the mucosa in the earliest stages that have been observed. It is extremely edematous and thick. Widely dilated small blood vessels are so numerous that it has the appearance of an unusually vascular granulation tissue. It is diffusely infiltrated by a cell-rich exudate, in which eosinophils abound. In more chronic stages much mature collagen is laid down. The diffuse exudate is replaced by a more focal reaction, with aggregates of mononuclear cells, which often resemble lymphatic follicles. Even in these stages some evidence of edema remains. The submucosal fibroplasia, perhaps even more than that in the mucosa, is a major cause of the thickening of the intestinal wall and the stenosis characterizing the chronic stages of regional enteritis (fig. 3).

Muscular Coats.—Exudative involvement of the heavy muscular coat is proportional to the activity in the two inner coats. In the earlier phases the most obvious change is the presence of mononuclear cells in focal deposits which seem to be associated with lymphatic channels. There

is only mild diffuse infiltration of the muscularis propria. The following features appear with chronicity: The muscular coats become thicker, their fibers are coarser and the neural elements in the wall are much more conspicuous. Groups of ganglion cells belonging to the plexus of Auerbach and their associated nerve fibers appear to be more abundant than in the uninvolved segments. It is possible that this is a relative increase, an increased prominence associated with contraction of the affected segment.

sclerosed and some appear to be occluded. The serosa is considerably thickened by edema and fibrosis, but increased prominence of blood vessels and of lymphatic channels likewise appears to play some part in this thickening. Of especial importance are the miliary serosal nodules found in so many of these patients.[2] These gave early observers the impression that the disease was tuberculous in origin, although tubercle bacilli could not be isolated. These nodules are miliary granulomas of nontuberculous origin con-

Fig. 5.—Giant cells lying in granulation tissue bordering a sinus tract.

However, there are regions which strongly suggest that there is a true neuromuscular hyperplasia, similar to that in the muscularis mucosae. These changes in the muscular and nervous elements are confined to the affected segments and are not found in the proximal (normal) segments or in the "skip areas," which lie between diseased segments. Even in the chronic stages there is comparatively little increase of connective tissue in the muscular layers.

Serosa.—In the serosa the evidence of involvement of the lymphatics becomes more definite. About the lymphatic channels are aggregates of lymphoid cells, and many of the channels are

sisting of inflammatory round cells, epithelioid cells and giant cells (fig. 4). Dispersed along the lymphatics of the serosa they form a middle link in the chain of lymphatic involvement so characteristic of this condition. This lymphatic involvement accounts for much of the edema, especially that of the later stages.

Mesentery and Lymph Nodes.—Progressing along the lymphatics into the mesentery of the bowel are focal accumulations of inflammatory cells grouped here and there about lymphatic channels. In these lymphoid aggregations may

2. Crohn, B. B., and Yunich, A. M.: Ileojejunitis, Ann. Surg. **113**:371, 1941.

be found giant cells just as they are seen in the intestinal wall and the lymph nodes. The extent of involvement of the mesentery is largely dependent on the presence of sinus tracts. These sinus tracts which arise from mucosal ulcerations may penetrate the mesentery, where they are seen as spaces lined by granulation tissue which contains numerous giant cells (fig. 5).

Pronouced lymphoid hyperplasia exists in the nodes draining the affected regions. This hyperplasia differs from simple hyperplasia in that one occasionally finds miliary tuberculoid granulomas containing giant cells within the nodes (fig. 6). Isolated giant cells, many of which contain particles of apparent vegetable material, may be seen in the lymph nodes, as well as in the granulation tissue bordering the sinus tracts.

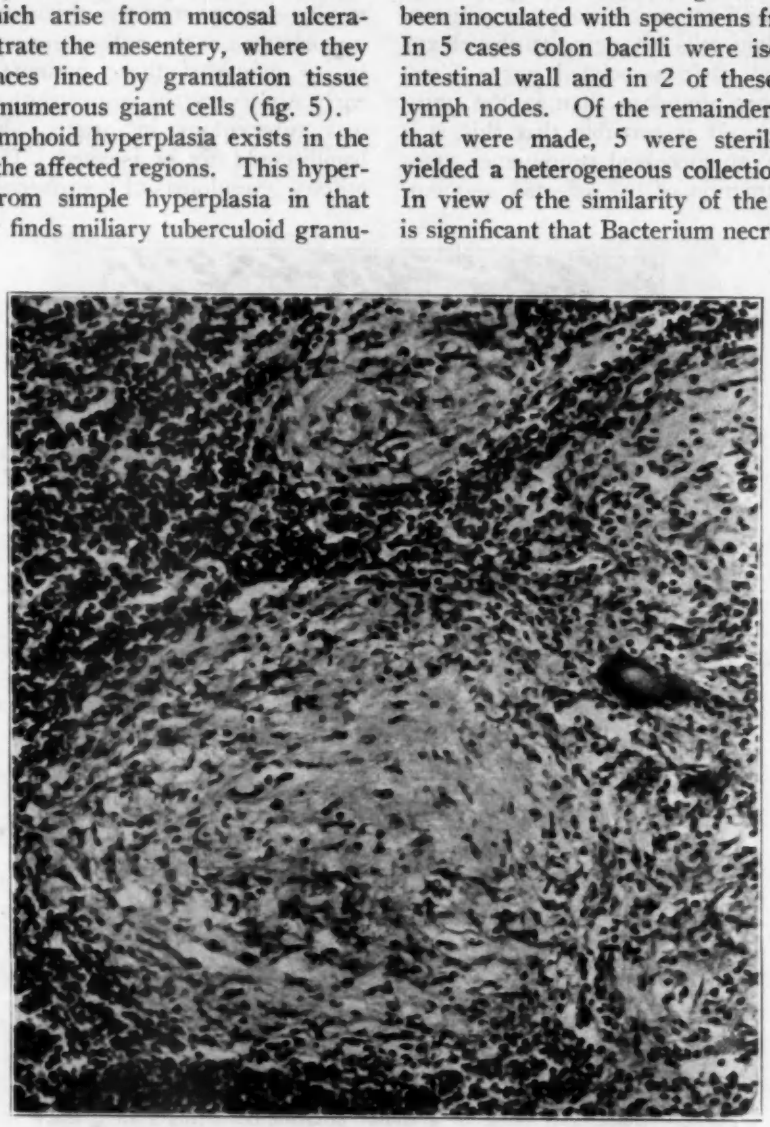

Fig. 6.—Tubercle contained within a mesenteric lymph node.

COMMENT

The uniformity of the microscopic characteristics observed in 22 cases of regional enteritis suggests a common causation for this entity. Although the etiologic agent has not been determined, this study suggests one or two possibilities.

In spite of determined efforts to isolate bacterial agents of disease from these specimens there have been no consistent findings. Tubercle bacilli were not found in guinea pigs which had been inoculated with specimens from 11 patients. In 5 cases colon bacilli were isolated from the intestinal wall and in 2 of these from adjacent lymph nodes. Of the remainder of the cultures that were made, 5 were sterile and the rest yielded a heterogeneous collection of organisms. In view of the similarity of the two diseases it is significant that Bacterium necrophorum, which Dragstedt, Dack and Kirsner[3] were able to isolate from the diseased colon and also from the mesenteric lymph glands in a majority of cases of chronic ulcerative colitis, was not found in regional enteritis, although methods for its detection were rigorously applied.

Cutaneous tests with Frei antigen were done in 4 of the more recent cases, and all gave negative reactions. This result would tend to rule

3. Dragstedt, L. R.; Dack, G. M., and Kirsner, J. B.: Chronic Ulcerative Colitis: Summary of Evidence Implicating Bacterium Necrophorum as Etiologic Agent, Ann. Surg. **114**:653, 1941.

out the virus of lymphogranuloma venereum as the etiologic agent. Further examinations for parasites of pathogenic nature were consistently unsuccessful in 12 cases.

Although these results of bacteriologic examination in themselves are not striking, they are consistent with those obtained by other investigators who have been interested in this disease. There have been some reports from different regions of the isolation of similar strains of streptococci, but the glaring lack of any consistent ability to demonstrate these organisms on the part of many investigators is in itself significant. This search for an offending organism has been furthered by study of sections of this material treated with various types of special stains. The end result has been the inability to demonstrate any definite etiologic agent of organic nature.

The involvement of lymphatic channels suggests that an important cause of the changes in the intestinal wall may be the obstruction of lymphatic channels. This theory is supported by the observations of Reichert and Mathes,[4] who reported in 1936 that they were able to produce changes similar to those of regional enteritis by chronic lymphatic obstruction. These changes were produced in dogs by the injection of sclerosing agents into the lymphatics of the small intestine. It is possible that mesenteric lymphadenitis may in some way be a precursor of regional enteritis by setting up a chronic sclerosing reaction of the mesenteric lymphatics.[5]

However, the fact that pronounced neuromuscular hyperplasia is present in the involved portion of the bowel and is absent elsewhere may shed light on the causation of the disease. The factor of contraction must still be ruled out in accounting for the apparent increase of ganglion cells and the muscular hyperplasia. Further work must be done to determine with certainty the part played by longitudinal contraction of the bowel. But these neuromuscular changes appear to be proliferative rather than the effects of contraction. Whether there is a congenital abnormality of the innervation of the involved bowel to account for the neuromuscular changes cannot be said at the present time. The question of a localized allergic response as yet cannot be confirmed or denied and must be given fair consideration.

SUMMARY

A study of the microscopic features of 22 cases of regional enteritis revealed neuromuscular hyperplasia as a characteristic feature of the disease heretofore unreported. No conclusions can be reached as to the causation of the disease.

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RESULTS OF LONG TERM EXPERIMENTAL CONSTRICTION OF THE HEPATIC VEINS IN DOGS

CHARLES D. ARMSTRONG, M.D., AND VICTOR RICHARDS, M.D.
SAN FRANCISCO

We have recently had the opportunity of observing a patient who presented at one time both polycythemia and thrombosis of the hepatic veins. This combination occurs not infrequently and has aroused the interest of clinicians for many years.[1] Most authors have assumed that thrombosis of the hepatic veins in this instance is secondary to thrombocytosis and slowing of the blood flow, but Oppenheimer [1a] credited Weber with the suggestion that polycythemia may actually be the result of occlusion of the hepatic veins. We have been unable to trace this statement to the writings of Parkes Weber, although he mentioned [2] "erythrocytosis due to stasis not of cardiac or pulmonary origin."

We hoped to resolve experimentally the order of appearance of polycythemia and thrombosis of the hepatic veins. To do this we produced occlusion of the hepatic veins by mechanical means and subsequently studied the effects on the blood.

From the Department of Medicine (Dr. Armstrong) and the Department of Surgery (Dr. Richards), Stanford University School of Medicine.

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2. Weber, F. P.: Polycythaemia, Erythrocytoses and Erythraemia (Vaquez-Osler Syndrome), London, H. K. Lewis Co., 1921.

OPERATIVE METHODS OE OCCLUSION OF THE HEPATIC VEINS

Winternitz [3] ligated the hepatic veins in dogs and found no changes in the liver in a series of unfinished experiments. Other workers [4] placed aluminum bands about the inferior vena cava above the hepatic veins and reduced the lumen of the veins by approximately 50 per cent. Necrosis of the liver and ascites ensued, the extent depending on the degree of constriction of the vena cava. The liver reverted to normal six days after the bands were removed.

An effective operation for temporary occlusion of the hepatic veins was described and used by Simonds and Brandes.[5] Momentary occlusion of the veins caused a sudden drop in blood pressure and an abrupt return to normal. Longer constriction produced a fall in the concentration of hemoglobin and platelets in the blood, a decrease in blood sugar and blood calcium and an increase in coagulation time.[6] After seven to thirty minutes of obstruction of the hepatic veins the hepatic cells became edematous and granular and there were hyperemia and dilatation of the sinusoids,[7] which disappeared when the veins were released. Fibrosis of the central veins occurred after prolonged occlusion. It is stressed that the liver of the dog is resistant to anoxemia.[8]

3. Winternitz, M. C.: The Effect of Occlusion of the Various Hepatic Vessels upon the Liver, Bull. Johns Hopkins Hosp. **22**:396-404 (Nov.) 1911.

4. Zimmerman, H. M., and Hillsman, J. A.: Chronic Passive Congestion of the Liver, Arch. Path. **9**:1154-1163 (June) 1930.

5. Simonds, J. P., and Brandes, W. W.: Effect of Obstruction of the Hepatic Veins upon the Systemic Circulation, Am. J. Physiol. **72**:320-323 (April) 1925.

6. Brandes, W. W.: The Effect of the Mechanical Constriction of the Hepatic Veins, with Special Reference to the Coagulation of Blood, Arch. Int. Med. **44**:676-692 (Nov.) 1929.

7. Simonds, J. P., and Callaway, J. W.: Anatomical Changes in Livers of Dogs Following Mechanical Constriction of the Hepatic Veins, Am. J. Path. **8**:159-165 (March) 1932.

8. Simonds, J. P., and Jergesen, F. H.: Late Changes in the Liver Induced by Mechanical Obstruction of the Hepatic Veins, Arch. Path. **20**:571-581 (Oct.) 1935.

Using 9 adult dogs in good condition and under pentobarbital sodium anesthesia, we attempted to produce occlusion of the hepatic veins. The hepatic veins in the dog are numerous, thin walled, almost sinusoidal and quite inaccessible because of their posteromedial position over the dome of the liver. In each of our animals the occlusion was carried out through the abdominal cavity. We considered a transpleural-transdiaphragmatic route but have not actually used it.

Our initial technic followed the procedure described by Simonds and Brandes[5]; certain details were later modified as the result of experience. The abdomen was opened by a transverse incision dividing both rectus muscles. An occlusive ligature was passed through the foramen of Winslow, forward over the left dome of the liver, around the anterior edge of the falciform ligament and backward over the right dome of the liver. To reduce the occluded tissue to a minimum the triangular ligaments were divided. The tie was made at the foramen of Winslow, and the ligature was left in place. Six of our 9 animals died, from hemorrhage caused by an inadvertent tear of the liver, from simultaneous occlusion of the inferior vena cava or from complete rapid occlusion of only the hepatic veins. Dog 1 died because of accidental ligation of the inferior vena cava together with ligation of the hepatic veins. Dog 2 was killed a week after the operation because of an infection in the eye; its liver was histologically normal. In dogs 4 and 5 the hepatic veins were acutely and completely occluded with steel wire ligatures. Each animal died within twelve hours of the operation, and sections of the livers showed central hyperemia of the hepatic lobules. Sudden complete occlusion of the hepatic veins seemed incompatible with life of the animal. In dogs 7 and 8 fenestrated rubber catheters were passed as ligatures and collodion was injected into the catheters. We hoped to occlude the veins by a ring of collodion which would subsequently shrink, but each dog died. Dog 7 died of hemorrhage from a tear of the liver; dog 8 died twelve hours after the operation, and autopsy disclosed rocklike collodion masses about the hepatic veins and other masses indenting the right renal vein. The right kidney was engorged, and the inferior vena cava was engorged but not occluded.

Dogs 3, 6 and 9 survived. Dog 3 had an artery tape passed around the hepatic veins and tied tightly enough to occlude them incompletely. Dog 6 had an artery tape tied loosely about the veins and soluble collodion injected along the tape with a needle. In dog 9 the hepatic veins were incompletely occluded by a cellophane tape 5 mm. wide tied as snugly as possible without being torn.

LABORATORY METHODS OF STUDY

Each of the 3 surviving dogs was carefully observed during the postoperative period and maintained on a constant, well balanced diet. Complete studies on the blood of each animal were done before the operation and at intervals thereafter. Blood was drawn by venipuncture of a jugular or a leg vein and placed in a tube containing a measured amount of anticoagulant. Packed cell volumes were measured in Wintrobe hematocrit tubes, spun for fifteen minutes at 3,500 revolutions per minute. Determinations of hemoglobin were done with a Sahli hemoglobinometer, in which 100 per cent equals 17 Gm. of hemoglobin per hundred cubic centimeters. Plasma proteins were determined by the Kagan falling drop method. The electrophoretic fractionation of the serum proteins was done by Dr. Eloise Jameson according to Longsworth's modification[9] of Tiselius' method.[10] Cephalin-cholesterol flocculation tests[11] were done on the serum used for fractionation.

TABLE 1.—*Hemoglobin, Packed Cell Volume and Plasma Protein Values of Dog 3*

Comment	Hemoglobin in %	Packed Cell Volume in %		Plasma Proteins in Gm./100 Cc.
		R.B.C.	W.B.C.	
3 days preop.	110	52.5	...	6.7
1 hr. preop.	90	43	...	...
1 hr. postop.	104	..	...	...
18 hr. postop., vomiting	110	55.5	...	6.7
2 days postop.	88	35	1.0	6.7
3 days postop.	90	41	1.8	6.2
8 days postop., infection of the wound	92	48	1.8	6.2
13 days postop., healing of the wound	86	44	1.1	6.0
27 days postop.	99	49	1.1	...
36 days postop.	100	49	1.3	6.2
42 days postop.	98	47	1.0	...
50 days postop.	96	47	2.0	6.9
63 days postop.	90	45	1.2	6.4
73 days postop.	98	46	1.2	...
78 days postop.	101	47.5	1.0	...
83 days postop.	110	47	1.5	7.1
102 days postop.	110	48.3	1.1	6.8
114 days postop.	100	48	1.3	6.8
128 days postop.	100	47.1	1.8	6.5
147 days postop.	95	48	...	...
183 days postop.	101	48	1.4	6.8
235 days postop., serum taken for flocculation and electrophoretic partition	84	47	1.2	6.8
245 days postop., laparotomy, biopsy specimen of liver	76	43	2.3	7.8
246 days postop.	84	38	0.9	8.2
270 days postop., dog killed after laparotomy				

After each dog had survived the operation for more than six months, a second laparotomy was done in an effort to measure the pressure in the portal vein. The animals were then killed by thoracotomy, and the organs were removed from above downward with inclusion of the diaphragm. The ligature was identified with rela-

9. Longsworth, L. G.: A Modification of the Schlieren Method for Use in Electrophoretic Analysis, J. Am. Chem. Soc. **61**:529 (Feb.) 1939.

10. Tiselius, A.: Electrophoresis of Serum Globulin: II. Electrophoretic Analysis of Normal and Immune Sera, Biochem. J. **31**:1464-1477, (Sept.) 1937.

11. Hanger, F. M.: Serological Differentiation of Obstructive from Hepatogenous Jaundice by Flocculation of Cephalin Cholesterol Emulsions, J. Clin. Investigation **18**:261-269 (May) 1939.

tion to the hepatic veins and the inferior vena cava before sections were taken for histologic examination.

PROTOCOLS OF DOGS SURVIVING OPERATION

Dog 3.—A male mongrel (artery tape loosely tied about the hepatic veins) had an uneventful postoperative course (table 1, fig. 1). On the one hundred and ninety-

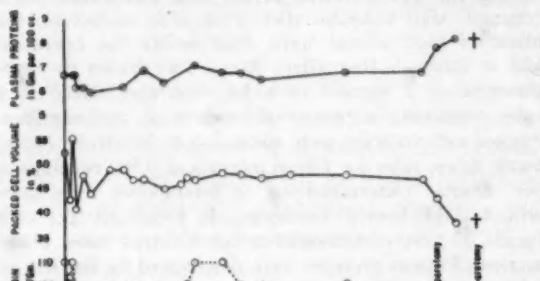

Fig. 1.—Changes in packed cell volume, hemoglobin and plasma proteins after obstruction of the hepatic veins of dog 3.

seventh postoperative day an exploratory laparotomy was done. The liver was normal in size and appearance, and biopsy sections were normal. The ligature was easily isolated but was covered with small adhesions. The pressure in the portal vein was 13 cm. of water. On the two hundred and thirty-second postoperative day laparotomy showed no change. The pressure in the portal vein was 9 cm. of water. Postmortem examination revealed that the ligature surrounded the hepatic veins but that their ostiums were widely patent. The liver weighed 360 Gm. The spleen was not enlarged. There was no evidence of collateral circulation. Sections

TABLE 2.—*Hemoglobin, Packed Cell Volume and Plasma Protein Values of Dog 6*

Comment	Hemoglobin in %	Packed Cell Volume in %		Plasma Proteins in Gm./100 Cc.
		R.B.C.	W.B.C.	
2 days preop.	82	46	...	6.0
5 days postop., vomiting for 3 days postop.	76	41	1.4	...
13 days postop., condition fair..	82	41	2.1	7.2
26 days postop., condition good	84	40	1.0	7.0
36 days postop., stitch abscess..	83	41	1.0	...
41 days postop., stitch abscess..	81	40	1.0	...
46 days postop., vomiting	87	41	1.8	7.9
64 days postop., condition good, no ascites	76	36.2	1.2	7.9
76 days postop.	76	36.5	1.3	7.9
90 days postop.	73	36	1.1	8.3
109 days opstop., listless	81	39	3.1	...
145 days postop., ? melena	68	31	1.7	7.3
197 days postop., vomiting, serum taken for flocculation tests and electrophoretic protein partition	56	29	1.1	8.8
207 days postop., losing weight, ascites	56	30.1	1.9	8.8
218 days postop., listless, ascites	42	26.1	1.1	8.6
228 days postop., dog killed after laparotomy	64	31	2.2	6.0

of liver showed no histologic abnormality except in the region of the ligature, which was surrounded by a thin layer of fibrous tissue, macrophages and foreign giant cells. Sections of spleen, kidney and bone marrow were not remarkable.

Dog 6.—A male bulldog (collodion-soaked artery tape tied about the hepatic veins) became progressively weaker after the third postoperative month, and ascites developed four months later (table 2, fig. 2). On the two hundred and twenty-eighth postoperative day laparotomy revealed a huge liver adherent to the abdominal wall and the diaphragm. The pressure in the portal vein was 35 cm. of water; that in the mesenteric vein, 16 cm. of water. Postmortem examination showed only the hepatic veins encircled by the ligature, which was encased in a dense, hard collar of fibrous tissue. This fibrous collar narrowed the lumens of the veins 20 to 30 per cent and weighed 76 Gm. The liver weighed 1,040 Gm. The right lobe of the liver contained an encapsulated cyst 5 cm. by 5 cm. by 5 cm., filled with gelatinous yellowish material. No hooklets were found. The spleen was not enlarged.

Histologic sections showed a hepatic vein surrounded by a broad zone of loose fibrous tissue densely infiltrated by inflammatory cells, many of which lay in small abscess cavities. The cells were largely macrophages, polymorphonuclear leukocytes and plasma cells. A gram

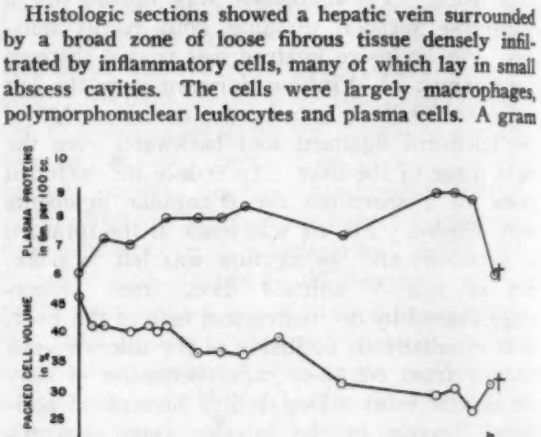

Fig. 2.—Changes in the packed cell volume, hemoglobin and plasma proteins after obstruction of the hepatic veins of dog 6.

stain revealed no bacteria. Adjacent hepatic tissue contained similar inflammatory cells extending among the cells, and scattered small ducts through the zone of inflammatory reaction suggested that hepatic tissue had been destroyed. Elsewhere in the liver there was slight dilatation of the sinusoids, in some places so great as to cause complete disappearance of the hepatic cell cords between adjacent sinusoids. In one area the hepatic tissue had been replaced by a mass of large, loosely placed endothelium-lined spaces filled with blood. Everywhere the structure of the liver was distorted by perisinusoidal deposition of amyloid, which compressed the hepatic cell cords. Sections of kidney showed moderate deposits of amyloid in the glomeruli, the interlobular spaces and the walls of small arteries. The spleen contained large masses of amyloid scattered irregularly through the red pulp.

Dog 9.—A female mongrel (cellophane tied about the hepatic veins) was in relatively poor condition at the time of operation but improved rapidly on a regular diet and ran a smooth postoperative course (table 3,

fig. 3). Laparotomy on the one hundred and eighty-sixth postoperative day revealed a large, scarred liver. There was no ascites, and the pressure in the portal vein was not taken. Postmortem examination showed that the ligature enclosed only the hepatic veins and encroached 10 to 20 per cent on their lumens. The liver weighed 575 Gm.; the spleen was not enlarged.

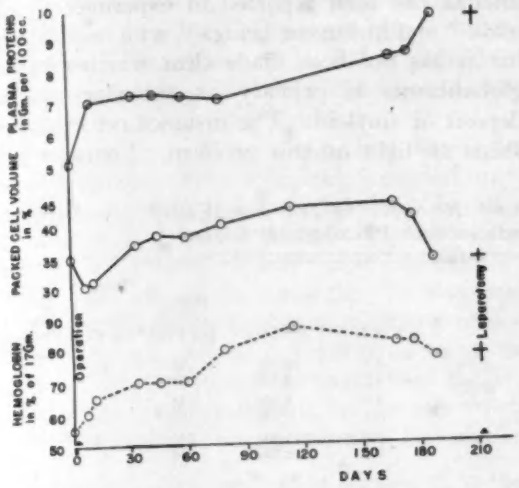

Fig. 3.—Changes in packed cell volume, hemoglobin and plasma proteins after obstruction of the hepatic veins of dog 9.

Histologically the ligature was embedded in pus surrounded by a thick zone of cellular connective tissue resembling that found in dog 6. Near the capsule of the liver were localized areas of moderately dilated sinusoids and atrophied hepatic cells without obvious relation to the hepatic lobules. Near the hilus of the liver there was a moderate diffuse atrophy of the hepatic cells, and many Kupffer cells contained hemosiderin. Sections of spleen and kidney were not remarkable.

TABLE 3.—*Hemoglobin, Packed Cell Volume and Plasma Protein Values of Dog 9*

Comment	Hemoglobin in %	Packed Cell Volume in % R.B.C.	Packed Cell Volume in % W.B.C.	Plasma Proteins in Gm./100 Cc.
2 days preop., dog thin and in poor condition	55	35	1.0	5.1
5 days postop., condition good	60	30.5	1.3	...
10 days postop.	65	31.1	1.1	7.0
33 days postop., vomiting once	70	37	1.1	7.2
45 days postop., condition good	70	38.2	1.8	7.2
59 days postop.	70	38	1.4	7.1
78 days postop.	80	40	...	7.0
114 days postop.	87	42.5	1.1	...
166 days postop., serum taken for flocculation test and electrophoretic protein fractionation	82	43	1.0	8.3
176 days postop., condition good	82	41	1.0	8.4
187 days postop.	77	34	1.0	9.6
211 days postop., dog killed after laparotomy				

RESULTS

The initial blood values of each dog and of a control dog on a similar diet are gathered in table 4. Serum for protein fractionations and flocculation tests was obtained from dog 3 on the two hundred and thirty-fifth postoperative day, from dog 6 on the one hundred and ninety-seventh and from dog 9 on the one hundred and sixty-sixth. Schlieren tracings of the electrophoretic patterns at two and one-half hours are reproduced in figure 4. The calculated protein fractions appear in table 5. Cephalin-cholesterol flocculation tests on the same serum yielded the results in table 5.

COMMENT ON RESULTS

The initial values of the packed cell volume of these dogs (table 4) have an average considerably higher than the 32.7 per cent reported by Kisch.[12] The average initial values of the plasma proteins are also somewhat higher than the averages of 4.9 Gm. per hundred cubic centimeters [13] and 6.2 Gm. per hundred cubic centimeters [14] found in other series. The packed cell volumes, red cell counts, hemoglobin values and plasma protein levels were higher in the male dog than in the female. Administration of pentobarbital

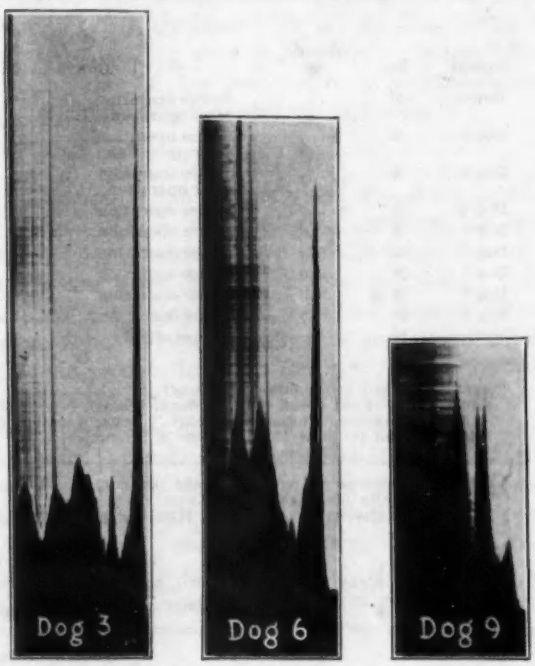

Fig. 4.—Schlieren tracings at two and one-half hours, showing results of electrophoretic protein fractionation in dogs surviving obstruction of the hepatic veins.

12. Kisch, B., and Strauss, E.: Hematocrit Readings of Normal Dogs, Exper. Med. & Surg. **1**:250-251 (Aug.) 1943.

13. Elman, R.: Acute Hypoproteinemia Following a Single Severe Hemorrhage in the Fasting Dog, Am. J. Physiol. **128**:332-337 (Jan.) 1940.

14. Achard, C.; Bariéty, M.; Codounis, A., and Hadjigeorges, E.: Amylose expérimentale et peturbation de l'équilibre protidique du sang chez le chien par injections intraveineuses de caséinate de soude, Compt. rend. Soc. de biol. **108**:702-704, 1931.

sodium produced in most instances an effect suggestive of hemodilution.

Polycythemia developed in none of the 3 dogs which survived attempts to ligate the hepatic veins. Although in each animal the procedure was different and a different degree of occlusion of the hepatic veins was thereby produced, these results support the popular view that polycythemia precedes thrombosis of the hepatic veins when the two conditions coexist.

Anemia and hyperproteinemia did develop in each of the surviving animals. These changes albuminuria of renal amyloidosis. Protein fractionation showed extreme hypoalbuminemia and hyperglobulinemia by virtue of increases in alpha and beta globulin; changes, in a word, similar to those reported by Longsworth and associates [15] in cases of obstructive jaundice. Hyperglobulinemia has been reported in experimental animals [16] and in human beings [17] with amyloidosis, but it has not been made clear whether hyperglobulinemia is primary or secondary to the deposit of amyloid. The instance reported here sheds no light on this problem. Leutscher's [17d]

TABLE 4.—*Initial Blood Values of All Experimental Dogs with Reference to Sex and Weight; Comparison of Values Before and After Anesthesia Induced with Pentobarbital Sodium*

Animal	Sex	Weight, Kg.	Comment	R.B.C.*	W.B.C.†	Hemoglobin, per Cent	Packed Cell Volume, per Cent	Plasma Protein‡
Dog 1	M	....	Before operation	4.9	10,175	82	42	...
			After operation	5.1	8,700	82	..	...
Dog 2	M	....	Before operation	5.6	8,550	84	..	...
			After operation	5.4	5,400	72	33	...
Dog 3	M	....	Before operation	6.0	15,500	110	52.5	6.7
			After operation	5.4	12,350	90	43	...
Dog 4	F	12.0	Before operation	...	.....	..	30	4.6
Dog 5	M	10.0	Before operation	6.3	.....	100	50	6.1
Dog 6	M	12.6	Before operation	6.4	.....	82	46	6.0
Dog 7	M	15.0	Before operation	7.4	.....	105	49	6.8
Dog 8	M	10.0	Before operation	6.5	.....	100	48	6.7
Dog 9	F	11.3	Before operation	4.6	.....	55	35	5.2
Control	M	....	No operation	...	.....	106	51.2	6.9
				Male and Female		Male		Female
Average packed cell volume (10 dogs)					43.6	46.4		32.5
Average initial red blood cells (10 dogs; 9 male, 1 female)					6.1	6.2		....
Average initial hemoglobin in per cent (9 dogs; 8 male, 1 female)					91.4	96.1		....
Initial plasma proteins (8 dogs; 6 male, 2 female)					6.0	6.4		4.8

* R.B.C. = millions of red blood cells per cu.mm. of blood.
† W.B.C. = white blood cells per cu.mm. of blood.
‡ Plasma proteins are expressed in Gm. per hundred cubic centimeters of blood.

TABLE 5.—*The Results of Cephalin-Cholesterol Flocculation Tests and Electrophoretic Fractionation of Proteins in Dogs Surviving Occlusion of the Hepatic Veins*

					Electrophoretic Fractionation (Calculated from Schlieren Diagram at 2½ Hr.)											
		Cephalin-Cholesterol Flocculation		Total Protein (Kagan)	Albumin	Albumin	α_1	Globulin	α_2	Globulin	β_1	Globulin	β_2	Globulin	γ	Globulin
Dog	Postoperative Day	24 Hr.	48 Hr.	Gm./100 Cc.	in %	in Gm.	in %	in Gm.	in %	in Gm.	in %	in Gm.	in %	in Gm.	in %	in Gm.
3	235	0	0	6.8	26.1	1.77	10.6	0.72	....	....	19.8	1.35	19.0	1.29	24.5	1.67
6	197	++	+++	8.8	10.1	0.88	15.6	1.37	13.4	1.18	33.6	2.96	18.5	1.63	8.8	0.78
9	166	0	±	8.3	32.07	2.66	6.08	0.50	3.42	0.28	31.96	2.65	....	....	26.5	2.21

appeared after seven months in the dog with a minimum of occlusion of the hepatic veins and hepatic damage (dog. 3). Electrophoretic fractionation of the proteins in this dog showed some hypoalbuminemia at a time when the total protein level was at the upper limit of normal. Progressive anemia and hyperproteinemia appeared in dog 6 one month after operation, but the interpretation of these changes is difficult because of the simultaneous, and probably fortuitous, development of amyloidosis in this animal. The terminal decline in total protein of the blood in this dog was probably due to the

15. Longsworth, L. G.; Shedlovsky, T., and MacInnes, D. A.: Electrophoretic Patterns of Normal and Pathological Human Blood Serum and Plasma, J. Exper. Med. **70**:399-413 (Oct.) 1939.

16. Achard et al.[14] Longsworth et al.[15]

17. (*a*) Eklund, C. M., and Reimann, H. A.: The Etiology of Amyloid Disease, Arch. Path. **21**:1-9 (Jan.) 1936. (*b*) Tiber, A. M.; Pearlman, A. W., and Cohen, S. E.: Hepatic Function in Patients with Amyloidosis, Arch. Int. Med. **68**:309-324 (Aug.) 1941. (*c*) Pearlman, A. W.: Amyloidosis: A Clinical and Pathological Study of One Hundred and Thirty-Five Cases, Quart. Bull., Sea View Hosp. **6**:295-308 (April) 1941. (*d*) Leutscher, J. A.: Electrophoretic Analysis of Plasma and Urinary Proteins, J. Clin. Investigation **19**:313-320 (March) 1940.

electrophoretic separations showed an increase in gamma globulin in a patient with amyloidosis.

Anemia and hyperproteinemia developed in dog 9 three to four months after operation. Here the electrophoretic pattern showed a moderate hypoalbuminemia, and the hyperglobulinemia was due to an increase in the beta and gamma globulin fractions. In dogs 6 and 9 a rise in plasma protein and a fall in packed cell volume foreshadowed future changes as early as the first postoperative week.

Kabat and co-workers [18] found that flocculation of cephalin-cholesterol mixtures depended on an increase in serum gamma globulin. In these animals flocculation was obtained only with serum in which the gamma globulins were relatively and absolutely reduced in amount. It was once widely accepted that cirrhosis or other forms of hepatic damage led to a diminution of serum protein. Recent writers have stressed the frequency of hyperglobulinemia in diseases of the liver.[19] Usually there is enough concomitant hypoalbuminemia so that the total protein level remains normal, but distinct increases in total protein may occur.[20] Hypoalbuminemia and hyperglobulinemia in the presence of damage to the liver suggest a principally hepatic source of serum albumin and a multiple origin of serum globulin.[21] Globulin may be formed in part in the cells of the reticuloendothelial system.[22]

Anemia and hyperproteinemia have not been reported in the obstruction of human hepatic veins; thus the human counterpart of this experimental syndrome is not available. It is probable, however, that hyperglobulinemia occurs in hepatic damage resulting from occlusion of the hepatic veins in human beings, and anemia is common with other forms of disease of the liver resulting in cirrhosis. Whipple has demonstrated a 40 per cent diminution of hemoglobin production factors with the hypoproteinemia (i. e., hypoalbuminemia) of cirrhosis.[23]

SUMMARY

Ligation of the hepatic veins was attempted in 9 dogs. Three survived the operation for two hundred and eleven, two hundred and twenty-eight and two hundred and seventy days. In each of these dogs anemia and hyperproteinemia developed. Hypoalbuminemia and hyperglobulinemia were demonstrated by electrophoretic fractionation of protein. The gross and histologic observations on each animal are described. Amyloidosis, probably unrelated to ligation of the hepatic veins, developed in 1 animal. These experiments suggest that polycythemia precedes thrombosis of the hepatic veins when the two diseases occur concomitantly. The concept of extrahepatic formation of serum globulin is supported.

18. Kabat, K. A.; Hanger, F. M.; Moore, D. H., and Landow, H.: Relation of Cephalin Flocculation and Colloidal Gold Reactions to Serum Proteins, J. Clin. Investigation **22**:563-568 (July) 1943.

19. (*a*) Loeb, R. F.: Plasma Proteins in Health and Disease, New England J. Med. **224**:980-987 (June 5) 1941. (*b*) Janeway, C. A.: The Plasma Proteins: Their Importance in Clinical Medicine and Surgery, ibid. **229**:751-756 (Nov. 11); 779-785 (Nov. 18) 1943. (*c*) Kagan, B. M.: Studies on the Clinical Significance of the Serum Proteins, Arch. Int. Med. **71**:157-163 (Feb.) 1943. (*d*) Jeghers, H., and Selesnick, S.: Hyperproteinemia: Its Significance, Internat. Clin. **3**: 248-279 (Sept.) 1937. (*e*) Bing, J.: Further Investigations on Hyperglobulinemia, Acta med. Scandinav. **103**:547-564 and 565-583, 1940. (*f*) Madden, S. C., and Whipple, G. H.: Plasma Proteins: Their Source Production and Utilization, Physiol. Rev. **20**:194-217 (April) 1940. (*g*) Casten, D.; Bodenheimer, M., and Barcham, I.: A Study of Plasma Protein Variations in Surgical Patients, Ann. Surg. **117**:52-73 (Jan.) 1943. (*h*) Cardon, L., and Atlas, D. H.: Incidence and Causes of Hyperproteinemia, Arch. Int. Med. **71**: 377-390 (March) 1943. (*i*) Post, J., and Patek, A. J.: Serum Proteins in Cirrhosis of the Liver: Relation to Prognosis and to Formation of Ascites, ibid. **69**:67-82 (Jan.) 1942; Nitrogen Balance Studies on Five Patients; ibid. **69**:83-89 (Jan.) 1942; (*j*) Serum Proteins in Relation to Liver Disorders, Bull. New York Acad. Med. **19**:815-830 (Dec.) 1943.

20. Amberg, S.: Hyperproteinemia with Severe Liver Damage, Proc. Staff Meet., Mayo Clin. **17**:360-362 (June 10) 1942. Cardon and Atlas.[19h]

21. Loeb.[19a] Madden and Whipple.[19f]

22. Loeb.[19a] Bing.[19e]

23. Whipple, G. H., and Robscheit-Robbins, F. S.: Hemoglobin Production Factors in Human Liver: Anemias, Hypoproteinemia, Cirrhosis, Pigment Abnormalities and Pregnancy, J. Exper. Med. **76**:283-298 (Sept.) 1942.

CHEMOSURGICAL TREATMENT OF CANCER OF THE LIP

A MICROSCOPICALLY CONTROLLED METHOD OF EXCISION

FREDERIC E. MOHS, M.D.
MADISON, WIS.

In the treatment of cancer of the lip a chemosurgical procedure offers certain important advantages. As previously described,[1] the chemosurgical method was devised to provide a microscopically controlled means for the excision of various accessible forms of cancer. The method entails, first, chemical fixation of the suspected tissues in situ and, second, systematic excision and microscopic examination of the fixed tissues. This process of fixation, excision and microscopic examination is repeated until a microscopically cancer-free surface is reached. The main advantages conferred by the microscopic control are (1) unprecedented reliability and (2) conservatism.

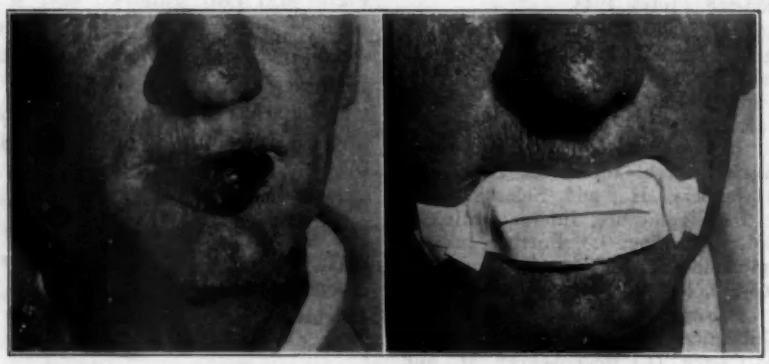

Fig. 1.—Example of dressing used for a large cancer of the lip.

TECHNIC

Preparatory to the first application of the fixative the skin surrounding the cancer of the lip is freshly shaved, all crusts and scales are removed from the surface of the tumor and a keratolytic, such as dichloroacetic acid or a saturated solution of trichloroacetic acid, is applied until the surface becomes white. Keratolysis is necessary to render the keratin layer permeable to zinc chloride. If the keratin layer is hard and thick it may be necessary to scrape the surface repeatedly and reapply the keratolytic.

The zinc chloride fixative is then applied to the cancer in a thickness varying from less than 1 mm. to 3 mm. or more, depending on the depth of penetration required. When the cancer is large the dose is at first correspondingly large, but as a cancer-free level is approached the dose is reduced. The formula of the fixative paste now used in our clinic is as follows [2]: 40 Gm. of stibnite (80 mesh sieve), 10 Gm. of powdered sanguinaria and 34.5 cc. of a saturated solution of zinc chloride.

The applied fixative is then covered with cotton, and this in turn is covered with an overlapping gauze-covered cotton dressing on which petrolatum has been spread to make it air tight. The dressing is then securely affixed with strips of quarter-inch or half-inch adhesive tape applied transversely and following the contour of the tumor (fig. 1). If the lesion extends back into

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From the Department of Surgery, Dr. E. R. Schmidt, chief, State of Wisconsin General Hospital and the McArdle Memorial Laboratory for Cancer Research.

1. (*a*) Mohs, F. E., and Guyer, M. F.: Pre-Excisional Fixation of Tissues in the Treatment of Cancer in Rats, Cancer Research **1**:49 (Jan.) 1941. (*b*) Mohs, F. E.: Chemosurgery: A Microscopically Controlled Method of Cancer Excision, Arch. Surg. **42**:279 (Feb.) 1941.

2. As previously pointed out,[1a] various other materials may be substituted for stibnite and for sanguinaria. The most satisfactory substitute for stibnite is made from clinkers from bituminous coal by grinding and passing them through an 80 mesh sieve. Rye flour is a satisfactory substitute for powdered sanguinaria.

the oral mucosa it is often desirable to place half-inch or 1 inch (1.25 or 2.5 cm.) tapes over the dressing in an anterior-posterior direction, extending from the skin of the chin externally to the gingivolabial sulcus internally. The tape in the latter position is held in place by the pressure between the teeth and the lip, though of course it does not adhere to the oral mucosa.

Dressings at the corner of the mouth are similar to those of the lower lip except that the half-inch tapes from the upper and lower lips and from the cheek converge on the mucosal side, where they are held in place by pressure between the cheek and the teeth. Dressings for the upper lip are similar to those of the lower lip.

The patient is then instructed to drink his liquids through a straw or a glass tube and to use care while eating to avoid undue soiling and movement of the dressing. Analgesics, varying from acetylsalicylic acid to codeine or even morphine, may be prescribed according to the extent of the lesion and the sensitivity to pain of the patient; often no analgesic is required. The patient usually remains ambulatory, often going about his business as usual.

After twenty-four hours the first layer of fixed tissue is excised with a scalpel (fig. 2 *A*, first excision). Since the incision is made through killed and fixed tissue, there is no pain or bleeding from this operation unless the incision is inadvertently carried too deeply. If bleeders are encountered they are controlled by applying a small square of gauze impregnated with the fixative under momentary pressure. Bleeding from the labial and the external maxillary artery can readily be stopped by this means.

After the first layer of tissue is excised it is usually possible to differentiate the fixed cancerous tissue, with its dead white color and crumbly consistency, from the fixed normal tissue, with its gray color and firm consistency. When cancer is thus grossly visualized, sections of the entire plane are unnecessary and only specimens for pathologic diagnosis are taken. If, however, the cancer is small, it is sometimes feasible to cut a section horizontally through the under surface of the first-removed specimen, and if this plane is free of cancer no further treatment is necessary.

When more cancerous tissue is known to be present the zinc chloride fixative is reapplied to the surface exposed by the first excision. Again the dose is judged to give the desired penetration. Twenty-four hours later another layer of tissue is excised (fig. 2 *A*, second incision). If, as in the diagramed example, the extensions of cancer at this level are small in caliber, they are invisible to the naked eye and their detection requires microscopic examination of the under surface of the excised layer.

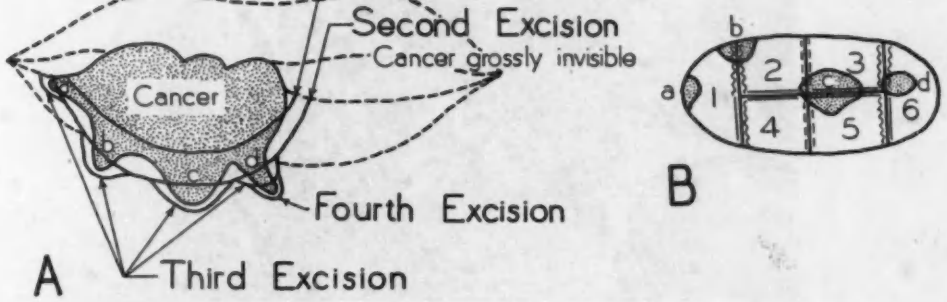

Fig. 2.—Diagram illustrating the chemosurgical technic: *A* (front view), cancer of the lower lip, indicated by stippled area, with outgrowths *a*, *b*, *c* and *d*. After daily chemical fixation of the tissues in situ, excisions are carried out at the four levels indicated. After the first excision the cancer (in this example) is grossly visible, but after the second excision the cancerous tissue cannot be recognized grossly. Therefore, the second excised layer is divided into specimens and mapped as shown in *B* (top view). Frozen sections cut through the under surface of the specimens reveal cancer in areas *a*, *b*, *c* and *d*, corresponding to the downgrowths in *A*. Only the cancerous areas are again fixed and excised, and the process is repeated until a cancer-free plane is reached.

This microscopic examination is accomplished by dividing the layer into specimens as it is removed. The edges of the specimens are marked with india ink, blue ink and mercurochrome for orientation (indicated by wavy, broken and solid lines respectively on the map in figure 2 *B*), and a map of each specimen is drawn on the lesion (with mercurochrome or ink) and on a pad of paper (fig. 2 *B*). The lesion is covered temporarily with moist cotton to prevent hardening of the surface while the frozen sections are being made and examined.

The specimens, having been fixed in situ, are usually firm and form retaining, and they are immediately cut through their under surfaces with a freezing microtome. The sections are stained with hematoxylin and eosin, cleared and mounted in clarite. The resulting sections, which have satisfactory microscopic detail for ready diagnosis (fig. 3), are immediately examined and the areas of cancer recorded on the map in red pencil. (Cancerous areas are stippled in figure 2 *B*). The india ink, blue ink and mercurochrome markings for orientation are readily visualized at the edges of the sections.

After the exact location of the remaining cancer has been determined the fixative is reapplied only to the cancerous areas. Twenty-four hours later another layer is excised from each of the treated areas (fig. 2 *A*, third excision), and the tissues still containing cancer are again treated and excised (fig. 2 *A*, fourth excision).

When a plane completely free of cancerous tissue is reached (e. g. fig. 5 *B*), the wound is covered with a gauze or cotton dressing spread with petrolatum to prevent excessive drying and shrinkage of the remaining thin layer of fixed tissue. Three days later this final layer of fixed tissue may be removed by snipping the holding strands of fibrous tissue with scissors (fig. 5 *C*). If desired, it may be left another day or so to separate spontaneously.

The resulting smooth, highly vascular, germ-resistant granulation tissue supports the exceptionally rapid growth of the epithelium across the wound. During healing it is optional either to apply a gauze dressing spread with petrolatum or simply to apply petrolatum directly to the undressed wound. As a result of the favorable conditions for healing, exceptionally comely scars and relatively slight deformities are obtained.

In advanced stages in which sufficient lip structure is removed to require a plastic repair, the tissues, because of their good vascular supply, lend themselves well to surgical procedures. Moreover, the preservation of a maximum amount of uninvolved tissue gives the surgeon more tissue with which to accomplish a favorable cosmetic result without the use of grafts.

THERAPEUTIC RESULTS IN CASES OF CANCER OF THE LOWER LIP

At the time of writing a total of 197 microscopically proved squamous cell carcinomas of the lower lip have been treated chemosurgically. However, a minimum of six months must elapse before any significance can be attached to the results. Accordingly, material in the following sections (up to the section on three year and five year results) concerns the cases of 176 consecutive patients admitted to the chemosurgery clinic between July 7, 1936 and May 29, 1943, the latter date being more than six months previous to the time of writing.

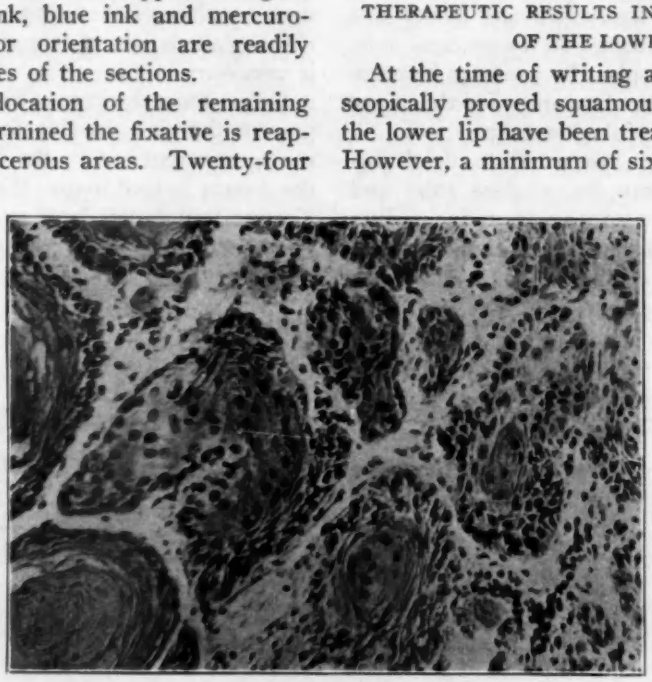

Fig. 3.—Photomicrograph of a squamous cell carcinoma of the lower lip which had been fixed in situ with zinc chloride. There was some shrinkage of cells, but the histologic diagnosis was readily made.

The lesions of these patients were in all stages. All but 4 of the 176 patients were men. The patients ranged from 22 to 91 years of age, with an average age of 62.6 years.

Primary Lesion.—Of the 176 squamous cell carcinomas of the lower lip treated chemosurgically, 172 primary lesions were completely eradicated (97.7 per cent) as far as can be determined at the time of writing by a careful follow-up for a period of from six months to over seven years. Chemosurgical treatment of 4 lesions was unsuccessful: Three were incompletely treated because when it became apparent that the cancer had invaded the entire body of

the mandible as well as the entire lip and chin, therapy was stopped at an optimal palliative level. The unsuccessful treatment of the fourth was due to the poor cooperation of a demented patient, who persistently removed the dressing from his advanced cancer; a surgical excision was therefore done, also without success. There were no failures that could be attributed to a fault in the method.

All but 2 of the 172 primary lesions were eradicated by the first series of treatments. Both of these were deep-seated carcinomas, recurrent after radium and roentgen therapy, in which outlying masses, disconnected from the original tumor, were present. These disconnected masses are occasionally found after part of a tumor has been killed by irradiation, and they constitute a hazard calling for more than usual care in check-ups following chemosurgical treatment. At any rate, these 2 carcinomas also finally responded successfully to subsequent chemosurgical treatment.

Regional Metastasis.—Metastasis to the regional lymph nodes occurred in 20 patients. Four of these were the previously mentioned patients with incompletely treated primary lesions, while the remaining 16 had no evidence of residual cancer at the primary site. Of these 16 patients, 6 had successful surgical dissections of the nodes by Dr. E. R. Schmidt and his staff; in 1 the nodes recurred after several chemosurgical and surgical dissections; 2 had partial chemosurgical dissections, but the nodes were found to be too extensive for complete removal; 1 had an unsuccessful surgical dissection two years later in another city; 4 received palliative roentgen therapy for inoperable nodes, while 2 patients refused any treatment for their nodes.

Of the 16 metastatic lesions in patients with controlled primary lesions only 5 became apparent after removal of the cancer of the lip. Thus, of 176 cases of this series in only 5 (2.8 per cent) was there involvement of nodes which made its clinical appearance after the chemosurgical treatment. This low incidence of metastasis confirms our previous findings that chemosurgical treatment has no tendency to increase metastasis in rats [1a] or in human beings.[1b]

In regard to the treatment of metastatic nodes, my present practice is to refer for surgical neck dissection all patients having freely movable metastatic nodes. Patients with nonpalpable nodes or with small, shotty, benign-feeling nodes are not subjected to prophylactic neck dissections unless the primary lesion is large and/or the microscopic grade of malignancy is high. When large, metastatic submental or submaxillary nodes are fixed to the mandible but there are yet no inoperable metastatic lesions evident in the cervical chain, I at times remove the mass chemosurgically as will be described later in this paper. Patients with hopelessly extensive metastatic nodes are usually referred for palliative roentgen therapy.

Fig. 4.—Example of primary lesion of group A (average diameter, under 1 cm.): *A*, squamous cell carcinoma in a young woman; *B*, granulations after removal of final layer of fixed tissue; *C*, healed lesion. The patient is free of cancer after four years.

End Results After Six Months or More.—While end results after six months are of limited use for the comparison of the chemosurgical method with other methods, they come within a very few per cent of indicating the true ultimate prognosis in regard to the cancer. The latter statement is true because residual foci of cancer, if left after chemosurgical treatment, make them-

selves apparent well within six months; they are not trapped deep in a surgical scar or in an atrophic radiation scar where they cannot be detected at an early date. Moreover, as mentioned previously, metastatic nodes rarely appear after chemosurgical removal of the primary lesion, and if they do they almost always appear within six months.

The 176 cases are divided into "indeterminate" and "determinate" groups. The indeterminate group includes those cases in which patients have died of intercurrent diseases without evidence of cancer and in which they have been lost from observation without cancer. The determinate group includes those cases in which patients have died of cancer, have been lost from observation with cancer or are living with cancer and those cases in which patients have been free of cancer for six months or more. For 1 patient who seemed well at his six and nine month check-up visits but who was reported to have a submaxillary mass later, treatment was counted as a failure.

For the 168 cases of the determinate group the cure rate after six months or more was 91.7 per cent (table 1).

Effect of Size of Primary Lesion on Prognosis.—In the 168 cases in the determinate group the primary lesions were divided into four groups according to their average diameter: A, under 1 cm. (fig. 4); B, 1 to 2 cm. (fig. 5); C, 2 to 3 cm. (figs. 6 and 8), and D, 3 cm. or more (fig. 7). The average size of all the cancers was 1.74 cm.

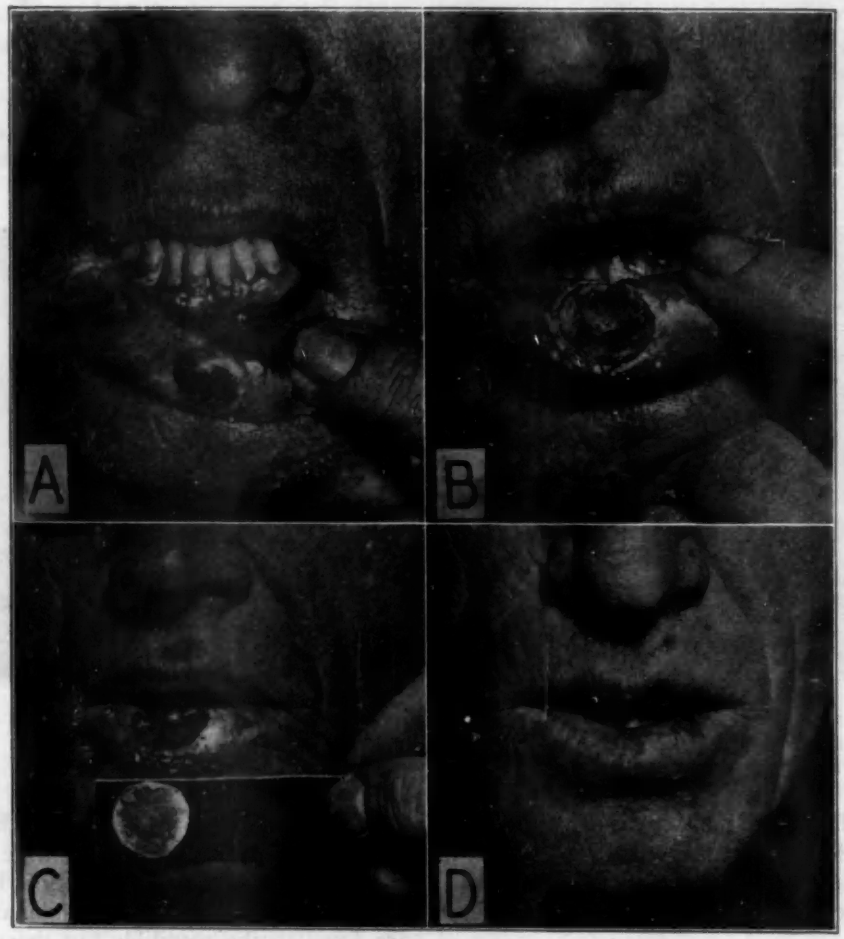

Fig. 5.—Example of primary lesion of group B (average diameter, 1 to 2 cm.): *A*, squamous cell carcinoma; *B*, area of fixed tissue at the microscopically cancer-free plane reached after three days; *C*, area of granulations and removed layer of fixed tissue four days later; *D*, healed lesion. The patient remains free of cancer after five years.

The end results in the four groups after six months or more indicate a striking correlation between the extent of the primary lesion and the prognosis (table 2). The less favorable results with increasing size are mainly due to the greater incidence of metastasis of the larger lesions,

but it is also of interest to note that the 4 primary lesions which were not eradicated were in group D.

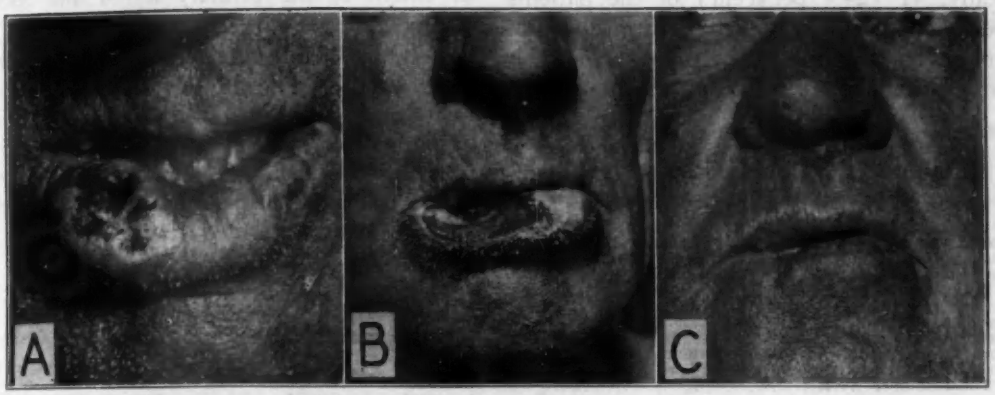

Fig. 6.—Example of primary lesion of group C (average diameter, 2 to 3 cm.): *A*, squamous cell carcinoma; *B*, granulations after removal of final layer of fixed tissue; *C*, healed lesion. Metastatic submaxillary nodes on the right side were partially resected surgically and then radically removed by the chemosurgical technic. The patient remains free of cancer after five years.

Fig. 7.—Example of primary lesions of group D (average diameter, 3 cm. or more): *A*, squamous cell carcinoma; *B*, granulations after removal of final layer of fixed tissue; *C*, healed lesion. The patient refused neck dissection; so he was referred for palliative roentgen therapy. The lip was free of cancer when last seen, ten months after treatment.

Fig. 8.—Example of primary lesion of group C at the commissure: *A*, squamous cell carcinoma involving mostly the upper lip but also the lower lip and the buccal mucosa at the corner of the mouth; *B*, granulations after removal of the final layer of fixed issue; *C*, healed lesion. The patient remains free of cancer after eighteen months.

Effect of Histologic Grade of Malignancy on Prognosis.—Classification of the 168 cancers of the lip on the basis of Broder's four grades of malignancy revealed a marked correlation between histologic structure and prognosis (table 3). The decreasing success of treatment with higher grades of malignancy is due mainly to the greater tendency of the undifferentiated cells to metastasize. Of the 4 primary lesions which could not be eradicated, 2 were of grade 2, 1 of grade 3 and 1 of grade 4.

Effect of Previous Treatment on Prognosis.—In the 168 cases in the determinate group in which cancers of the lip were treated chemosurgically, 41 (24.4 per cent) of the patients had been unsuccessfully treated by surgical operation, roentgen rays, radium or caustics, alone or in combination, before reporting to the chemosurgery clinic. While it was possible to salvage 33 (80.5 per cent) of these cases by the chemosurgical treatment, the cure rate was appreciably below the 95.3 per cent for the cases in which the patients had not been treated previously (table 4).

TABLE 1.—*End Results After Six Months or More in 176 Cases of Cancer of the Lower Lip*

This series includes the cases of all patients with histologically proved squamous cell carcinomas, both early and advanced, previously untreated and recurrent, with and without metastasis, who were admitted to the chemosurgery clinic from July 7, 1936 to May 29, 1943.

Total number of cases		176
Indeterminate group		
Patients dead from other causes without recurrence	1	
Patients lost from observation without recurrence	7	
Total number		8
Determinate group		
Total number		168
Unsuccessful results		
Patients dead as a result of cancer	9	
Patients lost from observation with cancer	3	
Patients living with cancer	2	
Total number		14
Successful results		
Patients free from cancer after six months or more		154
Six month end results		
Total number of cases with successful results divided by total number of determinate cases (154 ÷ 168)		91.7%

TABLE 2.—*Effect of Size of Primary Lesion on Prognosis*

Group	Average Diameter, Cm.	Number of Lesions	Successful Results: Number	Successful Results: Per Cent
A	Under 1	33	32	97.0
B	1-2	86	85	98.8
C	2-3	33	30	90.9
D	3 or more	16	7	43.8
All groups		168	154	91.7

TABLE 3.—*Effect of Histologic Grade of Malignancy on Prognosis*

Grade	Number of Lesions	Successful Results: Number	Successful Results: Per Cent
1	44	44	100.0
2	104	97	93.3
3	16	12	75.0
4	4	1	25.0

TABLE 4.—*Effect of Previous Unsuccessful Treatment on Prognosis*

	Number of Patients	Successful Results: Number	Successful Results: Per Cent
Previously untreated	127	121	95.3
Previously treated	41	33	80.5

The unfavorable effect of previous treatment is probably largely due to delay in eradication of the cancer of the lip, with a resulting increase in extent of the primary lesion and incidence of metastasis.

Effect of Metastasis Diagnosed at Onset of Treatment on Prognosis.—The most important factor in determining prognosis is the presence or absence of metastasis. Thus of the 15 cases in which submental, submaxillary or cervical metastases were diagnosed at the onset of chemosurgical treatment, only 4 (26.7 per cent) had a successful outcome, while of the 153 cases in which metastases were not found at that time successful results were obtained in 98 per cent (table 5).

TABLE 5.—*Effect of Metastasis Diagnosed at Onset of Treatment on Prognosis*

Metastasis Diagnosed at Onset of Treatment	Number	Successful Results: Number	Successful Results: Per Cent
Absent	153	150	98.0
Present	15	4	26.7

TABLE 6.—*Three Year and Five Year End Results of Cases of Cancer of the Lower Lip*

These series include the cases of all patients with histologically proved squamous cell carcinomas, both early and advanced, previously untreated and recurrent, with and without metastasis, who were admitted to the chemosurgery clinic from July 7, 1936 to Oct. 28, 1940 for the three year group and from July 7, 1936 to Nov. 19, 1938 for the five year group.

	Three Year Period	Five Year Period
Total number of cases	91	45
Indeterminate group		
Patients dead from other causes without recurrence	13	8
Patients lost from observation without recurrence	5	5
Total number	18	13
Determinate group		
Total number	73	32
Unsuccessful results		
Patients dead as a result of cancer	5	3
Patients lost from observation with cancer	2	1
Patients living with cancer	1	0
Total number	8	4
Successful results		
Patients free from cancer for three years or more (first column) or for five years or more (last column)	65	28
Three year end results		
Total number of cases with successful results divided by the total number of determinate cases (65 ÷ 73)	89%	
Five year end results		
Total number of cases with successful results divided by the total number of determinate cases (28 ÷ 32)		87.5%

Three Year and Five Year End Results.—Every effort is made to trace all patients for at least five years. There are, of course, the inevitable deaths from intercurrent disease and the patients lost from observation before the end of the three year or five year period. These patients' cases are included in the indeterminate group, after the example of Martin, MacComb

and Blady. The determinate group, on the other hand, includes those cases in which patients have died from cancer, been lost from observation with cancer or are living with cancer and those free from cancer after the three year or five year periods.

In the three year period successful results were obtained in 89 per cent of the 73 cases in the determinate group (table 6), and in the five year period, in 87.5 per cent of the 32 cases in this group (table 6).

THERAPEUTIC RESULTS IN CASES OF CANCER OF THE UPPER LIP

Eight patients with the relatively uncommon cancer of the upper lip (fig. 9) were treated in the chemosurgery clinic. A number of commissural lesions involved the upper lip to some extent (fig. 8), but reports of these are omitted here because they were included in the preceding series. There were 2 patients with unsuccessful results: 1 for whom chemosurgical treatment was temporarily stopped until another necessary operation could be performed, and who suddenly died of coronary occlusion before chemosurgical treatment could be resumed; 1 in whom cervical metastases developed which at the time of writing have recurred after two surgical dissections, although the upper lip remains free of cancer.

The end results after six months or more were successful for 5 of the 7 cases (71.4 per cent) in the determinate group. At the five year period results were successful for 2 of the 4 cases in the determinate group.

CHEMOSURGICAL TREATMENT OF INOPERABLE SUBMAXILLARY NODES

As previously mentioned, patients with regional metastases are referred for standard surgical dissections except for those with large submaxillary masses firmly adherent to the mandible and other structures (fig. 10). These fixed masses are removed chemosurgically if the grade of malignancy is not too great and if there are no inoperable lesions in the cervical chain.

The technic is essentially the same as that for the lesions on the lip, chemical fixation being carried to a microscopically cancer-free level. This procedure usually exposes at least the mandible, the submaxillary salivary gland and the mylohyoid and sternocleidomastoid muscles (fig. 10 *B*). The mandibular branch of the facial nerve is often interrupted. The cancer almost invariably involves the periosteum of the mandible, and in some cases the bone is eroded. The extent of involvement of bone can be seen grossly, which is fortunate, because it is of course impossible to make frozen sections of bone. However, specimens of soft tissue eroding the bone can be sectioned for confirmation of gross visualization. The zinc chloride fixative penetrates well through the bone, though somewhat more slowly than through soft tissues. The fixed bone is removed with a rongeur or a chisel. The process is repeated until solid, uninvolved osseous tissue is reached.

Fig. 9.—Squamous cell carcinoma of the upper lip: *A*, before, and *B*, after, chemosurgical treatment. The patient remains free of cancer after fifteen months.

After three or four weeks a line of demarcation forms under the remaining layer of fixed bone, and the sequestrum can then be grasped with a rongeur and lifted off the sound bone. The granulation tissue thus exposed supports the rapid growth of the skin across the wound. The resulting scar is not too disfiguring (fig. 10 *C*).

A total of 12 patients with inoperable submaxillary nodes were treated chemosurgically. The primary lesions had been removed by surgical operation and/or irradiation in all but 3 patients, who had been treated chemosurgically.

Five of the metastases were widespread, cauliflower-like masses, which were obviously hopeless but which were removed to relieve the patients temporarily of the large, malodorous lesions. Of the 7 remaining patients 1 was apparently free of cancer for one year (the patient died three years later of undetermined cause) and another appears to be free of cancer at the time of writing, after two years. In the other 5 either the mestastatic nodes proved to be too far advanced for complete removal or else cervical metastases were uncontrolled.

THERAPEUTIC RESULTS FOR OTHER NEOPLASMS OF THE LIP

The microscopic control of excision afforded by the chemosurgical method is also of value in assuring the complete removal of other neoplasms.

Basal Cell Carcinoma.—Most basal cell carcinomas involving the lip do so by invasion from an origin in the skin outside of the lip proper, but reports on these are omitted from this paper. Only one basal cell carcinoma originating in the lip was treated chemosurgically. It was a lesion 1.4 cm. in diameter on the lower lip. The patient was free of cancer after five years.

Hemangioma.—Half of the hemangiomas in this series were not diagnosed as such until the sections were examined, because when these lesions become ulcerated, hemorrhagic and crusted they often resemble cancer. All of the 8 hemangiomas treated chemosurgically were of the capillary type, and all involved the lower lip. None of them showed any evidence of recurring after from three months to five years.

Squamous Cell Papilloma.—Four papillated, hyperkeratotic lesions were removed from the lower lip by chemosurgical measures, with no return of the papillomas after periods of from seven months to four years.

Fibroma.—One fibroma of the lower lip was removed chemosurgically, and there was no evidence of it when the patient died of other causes after three months.

Epidermoid Cyst.—One post-traumatic epidermoid cyst was chemosurgically excised from the lower lip, with no return after seven months.

THERAPEUTIC RESULTS FOR PRECANCEROUS LESIONS OF THE LIP

In the prevention of cancer of the lip, the chemosurgical technic is of value as a simple and a reliable method for the eradication of precancerous lesions. The accurate histologic diagnosis afforded by the method is a distinct advantage, because it is often impossible to be sure clinically whether these lesions are precancerous or cancerous.

Fig. 10.—*A*, fixed submaxillary nodes secondary to a squamous cell carcinoma of the lower lip (the latter had been treated with radon seeds over a period of two years, after which a surgical resection and two plastic operations were done); *B*, after chemosurgical treatment, showing exposed mandible, mylohyoid muscle and sternocleidomastoid muscle; *C*, healed lesion. The patient showed no evidence of cancer when last seen one year later; he died of undetermined cause after three years.

The technic is essentially the same as that used in the treatment of cancer. Horizontal sections through the under surface of the first excised specimen are made to make sure there are no deeper downgrowths, and then the specimen is turned on edge, and vertical sections are made for diagnosis.

Precancerous Keratoses, Ulcers and Fissures.—These precancerous lesions are considered together because they grade into each other and seem to be simply different manifestations of the same process. The initial lesion is usually a keratosis—often starting as a localized scaly

or horny excrescence at one point in a narrow hyperkeratotic line extending across the entire lip. The adherent scale may be picked off by the patient or otherwise traumatized, forming an ulcer, which may heal temporarily but which more often persists and extends. In patients with clefts along the lower lip or at the commissures the ulcers may take the form of nonhealing fissures. Occasionally the granulations are so prominent that a diagnosis of granuloma pyogenicum is justified.

For a total of 44 patients these precancerous lesions of the lip were removed chemosurgically. Of these patients, 34 were followed for periods of from one month to seven years (average, two years). At the time of writing none of the lesions had recurred nor had the remaining tissue undergone malignant change. In none of the patients was there a defect in the lip, and the scars were practically invisible (fig. 11 *A*, *B*).

Leukoplakia.—Because leukoplakia presents a definite clinical and histologic entity (fig. 11 *C*, *D*) it is considered separately from the other precancerous lesions, though the hyperplasia and the hyperkeratosis in all of these conditions are probably essentially similar.

Sixteen patients with leukoplakia were treated chemosurgically. Ten were followed for periods of two months to six years (average, two years), and not a single instance of recurrence or malignant change was observed.

Radiation Ulcers.—The nonhealing ulcers which may result from roentgen or radium treatment of lesions of the lip may be classed as precancerous lesions. The purpose of the chemosurgical treatment of these lesions is to remove the poorly vascularized, scarred tissue so that prompt healing occurs.

Six radiation ulcers were treated chemosurgically, and of these 5 were followed from one month to seven years (average, thirteen months). Only 1 broke down after treatment, but further chemosurgical therapy healed it. None underwent malignant change.

COMMENTS

As previously stated, the microscopic control provided by the chemosurgical method is responsible for two important advantages in the treatment of cancer of the lip, namely (1) unprecedented reliability and (2) conservatism.

The great reliability of the method is attested by the fact that in 197 cases of cancer of the lower lip there were only 4 failures to eradicate the primary lesion and, as previously pointed out, none of these failures could be attributed to any fault of the method. This record was obtained despite the fact that 24.4 per cent of the primary lesions had earlier been unsuccessfully treated by other methods.

Moreover, the cure rate of 87.5 per cent after the five year period compares favorably with

Fig. 11.—Precancerous lesions: *A*, keratosis with ulceration and crusting; *B*, healed lesion two months after chemosurgical removal; *C*, leukoplakia; *D*, healed lesion thirteen months after chemosurgical removal.

that at the large, well known centers for the treatment of cancer in this and other countries. Thus the end results after five years given in recent years by workers from some of these institutions are as follows: Martin and associates [3] (1941), 70 per cent; Bergendal [4] (1938), 80 per cent; Schreiner and Christy [5] (1942), 75.7 per cent; Newell [6] (1939), 61.6 per cent, and Lacassagne [7] (1929), 58 per cent.

The conservatism of the method and the consequent cosmetic results are shown in the preceding photographs. Defects requiring subsequent plastic repair are obtained only when advanced lesions are removed. When defects result they usually are so minimal that most of the patients refuse the simple repair offered them.

The importance of the microscopic control afforded by the chemosurgical method was repeatedly brought home when, time after time, unsuspected outgrowths of small caliber from the main tumor mass were found microscopically, at times extending a considerable distance after becoming grossly invisible. In several instances the cancer extended along nerves picked up in the chin and followed them through the mental foramen and then for several centimeters along the inferior dental canal. A reconstruction of 1 cancer with such a tendency to follow nerves had the appearance of a pincushion on its under surface. More often, however, the slender outgrowths did not follow any specific structure but simply followed along planes of reduced resistance to their spread. Often the orbicularis oris muscle had slightly more resistance to the cancer than the softer tissues anterior and posterior to it, and the chemosurgical method allowed the preservation of a maximum amount of this structure.

The chemosurgical procedure carried practically no risk, even in elderly patients with advanced cancer of the lip. In no case was infection a problem, even though many of the patients had severe oral sepsis; the absence of infection was due to the sterilization of the lesion by the fixative during the treatment and to the resistance to germs of the granulation tissue after the separation of the final layer of fixed tissue. In fact, after chemosurgical treatment the dressings can safely be cared for by the patient himself. Hemorrhage during separation of the final layer of fixed tissue occurred in 3 patients of this series: Two hemorrhages were stopped within twenty minutes by the application of pressure and one was stopped by a suture-ligature.

The low incidence of metastasis appearing after chemosurgical removal of the primary lesion confirms our earlier impression [1] that chemical treatment of cancers has not the slightest tendency to cause further metastasis. Whether or not this method has less tendency to produce metastasis than surgical operation, with its handling factor, or irradiation, with its delay factor, cannot be determined with the statistics now at hand.

Chemosurgical treatment is particularly advantageous for cancer of the lip recurrent after surgical operation or irradiation. Such lesions often respond poorly to repetition of the original therapy, but they almost invariably respond to chemosurgical treatment.

This technic requires specialized training and a specially equipped clinic. It is my opinion that one such clinic should eventually be made available to every large center of population.

SUMMARY AND CONCLUSIONS

The chemosurgical treatment of cancer of the lip has the great advantage of microscopic control of excision. This feature accounts for the unprecedented reliability and the conservatism of the method.

The reliability of the method is indicated by the unusually high proportion of successful results after six months (91.5 per cent of 164 cases), after three years (89 per cent of 73 cases) and after five years (87.5 per cent of 32 cases). Although 24.6 per cent of the cancers of the lip had previously been unsuccessfully treated by other methods, 97.7 per cent of the primary lesions were eradicated by chemosurgical treatment.

The conservatism of the method allows preservation of a maximum amount of uninvolved lip tissue, with consequent excellent cosmetic results.

It is also an efficient treatment for carcinoma of the upper lip, for basal cell carcinoma, for various benign neoplasms and for precancerous lesions of the lip.

Firmly fixed submaxillary nodes constitute the only metastatic lesions for which chemosurgical treatment is indicated.

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EFFECTS OF CONTINUOUS AND OF INTERMITTENT APPLICATION OF A TOURNIQUET TO A TRAUMATIZED EXTREMITY

ALFRED BLALOCK, M.D.
BALTIMORE

It is generally recognized [1] that one should not employ a tourniquet for the control of bleeding if other means will suffice. If the use of a tourniquet is necessary, it is desirable to release it from time to time in order that some oxygen may be transported to the ischemic tissues. Unfortunately, the conditions in which the use of a tourniquet is required for the control of bleeding are usually such that intermittent release results in the loss of a prohibitive quantity of blood. Nevertheless, it appeared to be of interest to investigate experimentally the comparative effects of continuous and of intermittent application of a tourniquet to a traumatized extremity. In previous experiments [2] it was found that the application of a tourniquet to a traumatized extremity reduced the chances of survival of the animal. Additional studies [3] showed that cooling of the part distal to the tourniquet lessened the ill effects of the ischemia and the anemia.

Large animals were used in all studies. Anesthesia was induced by the intravenous administration of 30 mg. of pentobarbital sodium per kilogram of body weight. Additional injections of 5 mg. per kilogram were given as needed. Two experiments were performed simultaneously; in one the application of the tourniquet was continuous, and in the other it was intermittent. One of the posterior extremities was struck approximately four hundred and fifty moderately severe blows with a padded hammer. Immediately thereafter a tourniquet of heavy rubber tubing was applied tightly around the upper part of the thigh. In half of the experiments the tourniquet was left in place for five hours. The results of these experiments are given in table 1. In the other experiments the tourniquet was released for two minutes out of every thirty minutes during the five hour period. The results of these experiments are given in table 2.

The differences in the two groups of experiments were more marked than had been anticipated. Only 1 of the 13 animals survived in the group in which the tourniquet was left in place for five hours, whereas 8 of the 13 survived in the group in which the tourniquet was released intermittently. Other differences in the two groups are listed in table 3. These results simply confirm prevailing impressions in regard to the dangers associated with the prolonged use of a tourniquet on an injured extremity.

From the Department of Surgery of The Johns Hopkins University and Hospital. The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Offices of Scientific Research and Development and Johns Hopkins University.

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TABLE 1.—*Continuous Application of Tourniquet to a Traumatized Extremity*

Experiment No.	Body Weight, Kg.	Arterial Pressure, Mm. Hg					Hematocrit Reading					Urine			Hours Lived After Tourniquet Off	Loss of Fluid, % of Body Weight
		Control	5 Hr.	7 Hr.	9 Hr.	11 Hr.	Control	5 Hr.	7 Hr.	9 Hr.	11 Hr.	Volume, Cc. 5 Hr.	Volume, Cc. 5-9 Hr.	Casts		
6	10.8	153	173	68	52	...	46.6	44.9	62.5	62.9	....	16	5	0	5	5.23
8	12.1	128	138	65	...	...	43.9	48.6	66.2	66.1	....	20	2	+	4	4.95
10	12.7	128	158	118	108	108	37.8	34.8	54.2	52.8	....	13	12	0	Recovered	
12	9.5	133	118	110	90	48	38.8	39.2	45.1	44.4	42.0	23	16	+++	8	4.47
14	10.3	118	173	93	...	...	45.7	56.7	72.2	....	....	13	6	0	2	4.37
16	13.4	128	150	96	70	65	49.0	53.4	67.8	66.7	64.5	25	25	+++	13	5.71
18	15.4	153	153	70	30	...	52.4	52.4	67.4	69.7	....	30	2	0	4	3.73
20	12.1	118	150	98	...	...	46.7	40.3	54.7	....	....	31	5	+++	4	6.81
22	9.7	112	152	40	...	...	34.7	35.3	42.7	....	....	29	2	0	3	4.64
24	10.5	118	182	98	78	60	41.0	46.0	62.1	60.7	61.2	27	15	+++	9	4.52
26	9.2	128	152	75	45	40	45.7	47.2	52.9	52.6	51.4	25	12	++	7.5	4.89
28	13.6	130	148	72	...	...	43.8	45.0	65.9	69.8	....	31	3	+	4	6.06
				6 Hr.					6½ Hr.							
30	10.4	143	153	65	...	...	41.9	43.8	56.5	....	....	50	10	+	1.5	4.08

TABLE 2.—*Intermittent Application of Tourniquet to a Traumatized Extremity*

Experiment No.	Body Weight, Kg.	Arterial Pressure, Mm. Hg					Hematocrit Reading					Urine			Hours Lived After Tourniquet Off	Loss of Fluid, % of Body Weight
		Control	5 Hr.	7 Hr.	9 Hr.	11 Hr.	Control	5 Hr.	7 Hr.	9 Hr.	11 Hr.	Volume, Cc. 5 Hr.	Volume, Cc. 5-9 Hr.	Casts		
5	11.8	128	138	118	88	63	36.5	51.5	57.8	60.3	62.7	39	15	+++	9	4.09
7	12.0	123	163	113	90	88	42.9	52.4	57.7	56.8	56.6	15	15	0	Recovered	
9	11.1	118	78	45	...	...	43.6	46.8	47.0	45.0	....	17	6	+	4	3.82
11	9.4	118	133	80	68	60	38.0	43.2	47.3	46.4	45.4	26	6+	+++	9	3.99
13	11.5	143	108	100	90	75	49.7	59.4	62.0	60.4	60.7	5	8	0	Recovered	
15	11.4	118	158	133	128	113	40.0	51.8	52.8	53.1	53.2	39	31	0	Recovered	
17	15.3	115	160	103	93	88	36.2	44.1	46.3	45.7	46.5	22	12	++	Recovered	
19	11.8	112	148	128	98	98	40.3	44.3	46.8	43.5	45.0	25	36	0	Recovered	
21	9.4	105	133	72	62	42	37.4	42.9	45.1	45.3	45.1	22	4	+	7	6.12
23	10.5	133	170	102	123	128	50.8	51.7	50.8	61.2	63.1	39	27	0	Recovered	
25	10.7	138	148	128	98	92	44.6	47.3	53.3	52.2	51.0	21	44	0	Recovered	
27	15.4	118	152	142	138	128	35.8	38.4	45.8	47.5	48.6	42	36	0	Recovered	
29	8.8	130	133	98	83	63	53.0	55.2	59.6	57.9	58.6	20	7	+++	38	5.12

TABLE 3.—*Comparison of Effects of Continuous and of Intermittent Application of Tourniquets to Traumatized Extremities*

Observations	Continuous Application of Tourniquet (13 Experiments)	Intermittent Application of Tourniquet (13 Experiments)
Swelling of leg at end of 5 hour period	Very little	Marked
Extent of swelling several hours after release	Extensive, involving foot, ankle and groin	Limited in main to injured area
Color of skin after release	Blue	Beefy red
Knee reflexes after release	Absent	Present
Quantity of anesthetic agent	Less required	More required
Average increase of hematocrit reading at time of release (5 hour period)	1.5	6.2
Average increase of hematocrit reading 2 hours later (compared with control)	15.6	9.9
Output of urine after release of tourniquet	Very small amount	Moderate amount
Casts in urine	Moderate number	Very few
Average blood pressure (mm. Hg) just before end of 5 hour period	154	140
Average blood pressure 2 hours later	77	104
Number of animals surviving	1	8
Average period of survival of remainder	5+ hours	13+ hours
Regional loss of fluid, per cent of body weight	4.97 (12 experiments)	4.61 (5 experiments)

EFFECT OF HYPOPROTEINEMIA ON SUSCEPTIBILITY TO SHOCK RESULTING FROM HEMORRHAGE

COLONEL I. S. RAVDIN, CAPTAIN H. G. McNAMEE AND LIEUTENANT J. H. KAMHOLZ
MEDICAL CORPS, ARMY OF THE UNITED STATES
AND
J. E. RHOADS, M.D.
PHILADELPHIA

A positive relationship between hypoproteinemia and susceptibility to shock has been predicated on the observation that the hypoproteinemic animal is prone to have a decreased plasma volume [1] and that it is generally incapable of replacing any further loss in plasma protein rapidly because the stores of labile protein are largely exhausted. Little if any direct experimental evidence on this point has been reported, and yet the importance of this relationship is so practical, from the standpoint of both war surgery and civilian surgery, that the following experiments were undertaken with a view to establishing not only whether such a relationship does exist but whether it is quantitatively of sufficient importance to justify greater care in avoiding hypoproteinemia in persons who are likely to be exposed to shock-producing injuries.

METHOD

The experiments were carried out on mongrel dogs weighing 8 to 13 Kg. Hypoproteinemia was produced by repeated plasmaphereses in animals maintained on the following diet, which appeared to be adequate in all foods but protein. The amount offered was approximately 90 calories per kilogram per day to each dog, but in no instance did the animals eat all the food.

Diet

	Per Cent by Weight	Calories	Per Cent of Total Calories
Sucrose	55.1	220	44.7
Dextrose	18.17	73	14.7
Lard	23.19	200	40.6
Bone ash	2.36	...	....
Salt mixture	1.18	...	....
Total	100.0	493	100.0
Plus cod liver oil	1.5		

The following supplements (made up in an aqueous solution of about p_H 5) were fed separately from the preceding diet: 0.1 mg. of thiamine hydrochloride per kilogram per day; 400 mg. of Wilson's liver fraction E [2] per kilogram per day, and 50 mg. of choline chloride per kilogram per day. Each animal was given approximately 5 cc. daily. If most of the ration was consumed regularly they were mixed with the food; otherwise, when the intake of food was erratic, the supplements were given separately to insure their consumption.

The method of producing shock was similar to that used by Govier and Greer.[3] Successive amounts of blood were withdrawn from a femoral artery at fifteen minute intervals until the blood pressure remained below 60 mm. of mercury for thirty minutes. Measurements of the blood pressure were made in the femoral artery. In some instances continuous recordings were made with a kymograph. In other experiments the arterial pressure was measured against a column of mercury at the required intervals.

Experiments were completed with 5 normal animals and 6 hypoproteinemic animals. Four of the hypoproteinemic animals were allowed to recover for periods of one to seven months, at which time the serum protein concentration had in each instance returned to normal range for the species. The procedure for causing shock was carried out again on these animals with somewhat irregular results.

Loss of Blood Resulting in Depression of Blood Pressure to Below 60 Mm. of Mercury for Thirty Minutes

Normal Animals			Hypoproteinemic Animals			Hypoproteinemic Animals After Restoration of Serum Protein Level		
Dog No.	Serum Protein, Gm./100 Ml.	Loss of Blood, Ml./Kg.	Dog No.	Serum Protein, Gm./100 Ml.	Loss of Blood, Ml./Kg.	Dog No.	Serum Protein, Gm./100 Ml.	Loss of Blood, Ml./Kg.
127	6.1	51.9	102	4.1	25.6	102	6.4	26.7
473	5.3	48.1	41	3.0	25.2	41	6.8	23.5
493	6.2	37.9	182	3.7	28.7	182	7.2	44.4
686	5.5	48.1	207	3.5	25.9	796	7.6	39.2
739	5.9	48.0	796	2.9	32.8			
			797	3.8	27.7			

COMMENT

In experimental plasmaphereses in our laboratory it has been usual to bleed the animal to the first sign of air hunger and then to stop. It has been our observation that if the bleeding is continued much beyond this point the animal may die. As the procedure is repeated the amount of blood which may be drawn decreases progressively, so that as the serum protein concen-

From the Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania.

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tration approaches the edema level the amount of bleeding necessary to produce air hunger is about half the amount necessary when the first plasmapheresis is done.

Likewise, in clinical work it is often observed that patients who have to undergo a number of successive operative procedures react favorably at first and poorly later. This is particularly true of patients who have prolonged suppuration or prolonged drainage from a high intestinal fistula.

The well nourished, well developed, well rested person has always been recognized as a superior surgical subject. The precise factors which produce this superiority have never been clearly defined. It is probable that they are numerous, and it is also likely that the nutritional factors are important. We believe that for surgical patients protein nutrition is of especial importance. To what degree the presence of ample stores of protein conditions the body to withstand the hazards of surgical operation is impossible to state.

Earlier studies from this laboratory have demonstrated that hypoproteinemia interferes with healing of wounds,[4] and with gastric emptying,[5] retards intestinal motility [5a] and delays the calcification of callus in dogs following experimental fracture.[6] There is some evidence that it plays an important role in resistance to infection.[7]

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The present experiments indicate that hypoproteinemia of the degree produced increased the susceptibility to hemorrhagic shock about 67 per cent. That is, the mean loss of blood necessary to produce a standard effect on the circulation in the normal animals was 67 per cent greater than the mean loss of blood required to produce the same effect in the hypoproteinemic animals. Furthermore, the figures were rather consistent; the weakest normal animal withstood 5 cc. per kilogram more loss of blood than the strongest hypoproteinemic animal.

The animals whose protein had been restored, on the other hand, varied considerably in their responses. Dogs 152 and 41 went into shock as easily as they had when they were hypoproteinemic, even though the serum protein concentration had returned to normal. The other 2 animals, however, showed considerable improvement in their resistance to loss of blood. For dog 796 a much longer interval elapsed (seven) months), but for each of the other 3 animals the interval for recovery was about two months.

It should also be noted that some of the normal animals had serum protein concentrations a little below normal and yet withstood hemorrhage very well. All of these animals, however, had concentrations which were well above the level for edema for the dog.

These irregularities suggest that plasma protein levels near the normal range cannot be relied on to indicate the ability of the animal to withstand hemorrhage but that when severe hypoproteinemia is present it is probable that susceptibility to hemorrhagic shock is considerably increased.

CONCLUSIONS

Chronic hypoproteinemia caused a distinct increase in the susceptibility of dogs to shock due to hemorrhage.

Two of the dogs which had been hypoproteinemic appeared to remain hypersensitive to hemorrhage even after their serum protein had returned to a normal level.

INDEX TO VOLUME 48

Abdomen: See also Pelvis; Peritoneum; etc.
drepanocytosis (sicklemia) and apparently acute surgical condition of abdomen; report of their occurrence in white youth, with laparotomy, 123
penetrating wounds of, 311
significance of supraclavicular signal node in patients with abdominal and thoracic cancer; study of 122 cases, 169
traumatic retroperitoneal rupture of duodenum; presentation of case and review of literature, 372
Abnormalities and Deformities: See also under names of diseases, organs and regions, as Epididymis; Kidneys; etc.
developmental anomalies, 169
fracture deformities, 259
Abscess: See under names of organs and regions, as Thyroid; etc.
Acid, Pyruvic: See under Blood
Acromioclavicular Joint: See Shoulder
Actinomycosis of kidney, 330
Adams, W. E.: Hemangioma of mediastinum; report of case, 126
Adrenals, cortical tumors, 331
disease, and pseudohermaphroditism, 333
medullary tumors, 332
Age, Old: See Old Age
Albumin: See Albuminuria; Blood, proteins; Proteins
Albuminuria, orthostatic, 156
Allergy: See Anaphylaxis and Allergy
American Academy of Orthopaedic Surgeons, progress in orthopedic surgery for 1942; preface, 266
progress in orthopedic surgery for 1942; review prepared by editorial board of, 89, 166, 229
Amputation, finger amputation, 175
Anaphylaxis and Allergy, role of allergy in delayed healing and in disruption of wounds; antigenicity of catgut, 438
role of allergy in delayed healing and in disruption of wounds; delayed healing and disruption produced by local allergic reaction (Auer phenomenon), 450
role of allergy in delayed healing and in disruption of wounds; effect of specific sensitivity to catgut on reaction of tissues to catgut sutures and on healing of wounds in presence of catgut sutures, 445
Anemia, sickle cell; drepanocytosis (sicklemia) and apparently acute surgical condition of abdomen; report of their occurrence in white youth, with laparotomy, 123
splenic; hip joint involvement in Gaucher's disease, 168
Anesthesia, 354. See also Surgery
Anesthetics: See Anesthesia
Aneurysm, renal, 330
Angioma, renal lesions in von Hippel-Lindau disease, 352
Ankle: See also Astragalus; Foot
conditions of foot and ankle, 89
dislocations of, 240
injuries, 98
sprains, 98
Anomalies: See Abnormalities and Deformities; and under names of diseases, organs and regions
Antigens and Antibodies, role of allergy in delayed healing and in disruption of wounds; antigenicity of catgut, 438
role of allergy in delayed healing and in disruption of wounds; delayed healing and disruption produced by local allergic reaction (Auer phenomenon), 450
Anuria: See Urine, suppression
Apparatus for measuring rate of enzymatic digestion of absorbable surgical sutures and other protein fibers, 120
Armies: See Military Medicine
Arms: See Extremities; Forearm; Humerus; Radius; etc.
Armstrong, C. D.: Results of long term experimental constriction of hepatic veins in dogs, 472
Arteries: See also Aneurysm; Blood, pressure; Thrombosis; etc.
injuries to, 312
Ascitic Fluid, renal operation for drainage of, 330
Astragalus: See also Ankle
fractures of, 241
Atrophy: See under names of organs and regions, as Bones, atrophy; etc.
Auer Phenomenon, role of allergy in delayed healing and in disruption of wounds; delayed healing and disruption produced by local allergic reaction (Auer phenomenon), 450

Bacilluria: See Urine, bacteria
Bacteria: See Tubercle Bacilli; etc.
Baker, R. D.: Untoward effects of various substances recommended for burns or wounds; experimental tests on rats, 300
Bauer, F. K.: Vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; hepatic disease, 185
Vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; renal disease, neoplastic disease and infection, 193
Vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; thyroid disease, 190
Berg, P., Jr.: Tuberculous abscess of thyroid gland; report of case and review of literature, 429
Bilharziasis: See Schistosomiasis
Biliary Tract: See Liver
Blackman, S. S., Jr.: Lateral aberrant thyroid; metastasis to lymph nodes from primary carcinoma of thyroid gland, 223
Bladder: See also Urinary Tract
calculus, 336
carcinoma, 337
cystitis emphysematosa, 341
diverticula, 340
diverticula and prostatic obstruction, 149
malakoplakia, 88
neural lesions, 342
neurogenic conditions, 88
radiation injuries, 88
rupture, 87, 339
tumor, 84
Blalock, A.: Effect of continuous and of intermittent application of tourniquet to traumatized extremity, 489
Blastomycosis involving epididymis, 350
Bloch, R. G.: Hemangioma of mediastinum; report of case, 126
Blood: See also Anemia; etc.
coagulation; application of dicoumarin (3-3'-methylene-bis-[4-hydroxycoumarin]) in trauma and gangrene, 1
coagulation; nervous regulation of clotting mechanism, 105
pressure, high; hypertension, 329
proteins; effect of hypoproteinemia on susceptibility to shock resulting from hemorrhage, 491
proteins; hypoproteinemia; clinical relationship of proteins and protein metabolism to therapy with reference to surgery, 36
transfusion; comparative value of some blood substitutes used for treatment of experimental shock, 315
vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; hepatic disease, 185
vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; renal disease, neoplastic disease and infection, 193
vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; thyroid disease, 190
volume; toxicopathologic studies on dye T-1824, 17
Blount, W. P.: Conditions involving elbow, forearm, wrist and hand, 169
Bones: See also under names of bones
atrophy; post-traumatic painful osteoporosis, 259
bone and cartilage transplants, 262
changes in osseous tissues after prolonged administration of estradiol benzoate (estrogen), 180
classification, 178
Deformities: See Abnormalities and Deformities; etc.
Diseases: See Osteochondritis; Osteomyelitis; etc.

Bones—Continued
Dystrophy: See Bones, atrophy; Bones, growth
Fractures: See Fractures
grafts, 265
growth, and endocrines, 179
influence of estrogens on shape of long bones, 181
Brain: See Nervous System; etc.
Brambel, C. E.: Application of dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]) in trauma and gangrene, 1
Breast, prosthetic restorations for; technic using sponge rubber, 388
Brewer, J. H.: Casein in local treatment of burns and wounds, 130
Brown, A. M.: Prosthetic restorations for breast; technic using sponge rubber, 388
Brunschwig, A.: Intravenous administration of fat for nutritional purposes; experimental study, 395
Burns, casein in local treatment of burns and wounds, 130
heat and mustard gas burns; comparison, 284
treatment, 310
untoward effects of various substances recommended for burns or wounds; experimental tests on rats, 300
Bursa, syphilis of tendon of long head of biceps muscle and of olecranon bursa, 423

Calcaneum, fractures of, 241
Calcification: See Bones, growth; etc
Calcium and Calcium Compounds, calcium deposits, 173
Calculi: See Bladder; Kidneys; Pancreas; Ureters; Urinary Tract; etc.
Callus: See under Fractures
Canby, C. B.: Drepanocytosis (sicklemia) and apparently acute surgical condition of abdomen; report of their occurrence in white youth, with laparotomy, 123
Cancer: See also Tumors; and under names of organs and regions, as Abdomen; Bladder; Colon; Lips; Prostate; Thyroid; Ureters; etc.
vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; renal disease, neoplastic disease and infection, 193
Carbuncle, Renal: See Nephritis
Carcinoma: See Cancer
Cardiovascular System: See Arteries; Heart; etc.
Carpenter, G.: Drepanocytosis (sicklemia) and apparently acute surgical condition of abdomen; report of their occurrence in white youth, with laparotomy, 123
Carpus: See Wrist
Cartilage, 181. See also Osteochondritis; etc.
bone and cartilage transplants, 262
reconstructive plastic surgery of absent ear with necrocartilage; original method, 53
Caruncle: See Urethra
Casein in local treatment of burns and wounds, 130
Casts: See Fractures
Catgut: See Sutures
Cells: See also Tissue
interstitial cell tumors of testis; report of 3 new cases, 415
Chemosurgery: See Lips, cancer
Chemotherapy: See Sulfonamides
Chest: See Thorax
Chondrogenesis: See under Cartilage
Clavicle, fractures of, 229
significance of supraclavicular signal node in patients with abdominal and thoracic cancer; study of 122 cases, 109
Clay, R. C.: Giant nevus of thigh successfully treated by complete excision and primary grafting, 319
Lateral aberrant thyroid; metastasis to lymph nodes from primary carcinoma of thyroid gland, 223
Lobectomy of liver; report of 3 cases, 267
Colles Fracture: See Radius, fractures
Colon: See also Intestines
Fistula: See Fistula
two stage operation for carcinoma of transverse colon producing duodenocolic fistula; report of 2 cases, 197; correction, 371
Contracture, Dupuytren's, 177
Volkmann's ischemic contracture, 170
Convalescence; convalescent care of patients with fractures, 253
Convulsions: See Epilepsy
Conwell, H. E.: Fractures excepting fractures of neck of femur, 229
Cook, E. N.: Review of urologic surgery, 73, 146, 325
Coumarin, application of dicoumarin (3-3'-methylene-bis-[4-hydroxycoumarin]) in trauma and gangrene, 1
Crile, G.: Naval casualties in base hospital in South Pacific, 305
Cryptorchidism: See Testes, undescended
Curtis, R. M.: Casein in local treatment of burns and wounds, 130
Cystitis: See under Bladder
Cysts: See under names of organs and regions, as Kidneys; etc.

Davis, H. A.: Vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; hepatic disease, 185
Vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; renal disease, neoplastic disease and infection, 193
Vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; thyroid disease, 190
Deformities: See Abnormalities and Deformities; and under names of diseases, organs and regions
de Takáts, G.: Nervous regulation of clotting mechanism, 105
Detergents, untoward effects of various substances recommended for burns or wounds; experimental tests on rats, 300
Dicoumarin: See Coumarin
Diethylstilbestrol: See Estrogens
Digestive System: See Intestines: Pancreas; etc.
Dislocations: See Ankle; Hip; Shoulder; etc.
Diverticula: See Bladder; Urethra
Dockerty, M. B.: Mediastinal ganglioneuroma, 208
Drepanocytosis: See Anemia, sickle cell
Dunham, L. J.: Intravenous administration of fat for nutritional purposes; experimental study, 395
Duodenum, Fistula: See Fistula
traumatic retroperitoneal rupture; presentation of case and review of literature, 372
Dupuytren Contracture: See Contracture
Dystrophy: See Bones, atrophy

Ear, reconstructive plastic surgery of absent ear with necrocartilage; original method, 53
Edmondson, H. A.: Interstitial cell tumors of testis; report of 3 new cases, 415
Elbow, conditions involving elbow, forearm, wrist and hand, 169
fractures about, 230
tendon ruptures about elbow, 170
Ellmore, L. F.: Drepanocytosis (sicklemia) and apparently acute surgical condition of abdomen; report of their occurrence in white youth, with laparotomy, 123
Embolism: See Thrombosis
Emphysema, cystitis emphysematosa, 341
Endocrine Glands and growth of bones, 179
Endocrine Therapy: See under names of glands and hormones
Enteritis: See Intestines
Enzymes, apparatus for measuring rate of enzymatic digestion of absorbable surgical sutures and other protein fibers, 120
Epididymis, abnormalities; polyorchidism, 350
blastomycosis involving, 350
tumor, 350
tumor and tunica vaginalis, 158
Epilepsy, question of vertebral fractures in convulsive therapy and in epilepsy, 244
Epiphyses, epiphyseal pseudarthrosis, 264
epiphysial separations, 252
Erythremia: See Polycythemia
Erythrocytes: See Anemia; etc
Estradiol Benzoate: See Estrogens
Estrogens, changes in osseous tissues after prolonged administration of estradiol benzoate (estrogen), 180
influence on shape of long bones, 181
oral administration of diethylstilbestrol for prostatism; clinical evaluation, 381
Evans Blue, toxicopathologic studies on dye T-1824, 17
Exophthalmos, progressive, in toxic disease of thyroid gland; review of recent literature, with report of case of progressive post-thyroidectomy proptosis in 6 year old Negro girl, 214
Extremities: See also under names of bones
Amputation: See Amputation
application of dicoumarin (3-3'-methylene-bis-[4-hydroxycoumarin]) in trauma and gangrene, 1
effects of continuous and of intermittent application of tourniquet to traumatized extremity, 489

Fat, intravenous administration for nutritional purposes; experimental study, 395
Femur: See also Hip
Epiphyses: See Epiphyses
fractures of, 236
fractures of neck of, 253
Ficarra, B. J.: Pancreatic calculi; report of 7 cases in 2 of which cure was effected by pancreaticolithotomy, 137
Fingers and Toes: See also Foot; Hand
Contracture: See under Contracture
correction of opponens paralysis, 176
finger amputation, 175
hallux valgus, 97
Fistula, two stage operation for carcinoma of transverse colon producing duodenocolic fistula; report of 2 cases, 197; correction, 371
vesicointestinal, 87
vesicovaginal, 342
Flatfoot: See Foot, deformities
Foot: See also Ankle; Astragalus; Calcaneum; Fingers and Toes; Metatarsus; etc.
and military service, 92
conditions of foot and ankle, 89
deformities, 94
disorders; conditions of foot and ankle, 89
fractures and dislocations of bones of hands and feet, 235
fractures; march fractures, 251
March: See Metatarsus
Forearm, conditions involving elbow, forearm, wrist and hand, 169
fractures of, 233
reconstruction following partial resection of radius, 263
Foreign Bodies, 309
in renal pelvis, 79
Fractures: See also Forearms ; Jaws; Pelvis; Spine; and under names of bones and joints, as Astragalus; Calcaneum; Elbow; Femur; Hip; Humerus; Metatarsus; Patella; Radius; Scaphoid Bone, Carpal; Tibia; Ulna; etc.
Colles: See Radius, fractures
compound, 247
convalescent care of patients, 253
delay in union of, 265
excepting fractures of neck of femur, 229
external skeletal pin fixation for, 252
formation of callus and healing of, 261
fracture deformities, 259
march fracture, 251
pathologic, 251
post-traumatic painful osteoporosis, 259
Frostbite, application of dicoumarin (3-3'-methylene-bis-[4-hydroxycoumarin]) in trauma and gangrene, 1

Ganglioneuroma, mediastinal, 208
Gangrene, application of dicoumarin (3-3'-methylene-bis-[4-hydroxycoumarin]) in trauma and gangrene, 1
gas, and tetanus, 313
progressive, in operative wound, 457
Gas, Gangrene: See Gangrene
heat and mustard gas burns; comparison, 284
Gastrointestinal Tract: See Colon; Intestines; etc.
Gaucher's Disease: See Anemia, splenic
Genitals: See Urinary Tract; and under names of genitals, as Penis; etc.
Genitourinary Tract: See also Urinary Tract
Globulin in Blood: See Blood, proteins
Goiter: See also Thyroid
goiter heart; experimental study, 27
Gonorrhea, sulfonamide and penicillin therapy, 162
Grafts, bone, 265
giant nevus of thigh successfully treated by complete excision and primary grafting, 319
Gray, H. K.: Mediastinal ganglioneuroma, 208
Gunshot Wounds: See Wounds
Gutierrez, R.: Review of urologic surgery, 73, 146, 325
Gynecology, ureteral injury during gynecologic operations, 335

Haik, G. M.: Progressive exophthalmos in toxic disease of thyroid gland; review of recent literature, with report of case of progressive postthyroidectomy proptosis in 6 year old Negro girl, 214
Hallux: See Fingers and Toes
Hammack, R. W.: Interstitial cell tumors of testis; report of 3 new cases, 415
Hand: See also Fingers and Toes
conditions involving elbow, forearm, wrist and hand, 169
fractures and dislocations of bones of hands and feet, 235
surgery of, 174
Hauser, E. D. W.: Conditions of foot and ankle, 89
Heart, goiter heart; experimental study, 27
Heat and mustard gas burns; comparison, 284
Hellwig, C. A.: Goiter heart; experimental study, 27
Hemangioma of mediastinum; report of case, 126
Hemorrhage, effect of hypoproteinemia on susceptibility to shock resulting from hemorrhage, 491
effects of continuous and of intermittent application of tourniquet to traumatized extremity, 489
Hemorrhoids, administration of succinylsulfathiazole before and after hemorrhoidectomy, 366
Hemostasis: See also Blood, coagulation; etc.
effects of continuous and of intermittent application of tourniquet to traumatized extremity, 489
Henry, M. G.: Fractures of carpal scaphoid bone in industry and in military service, 278
Heparin, nervous regulation of clotting mechanism, 105
Hepler, A. B.: Review of urologic surgery, 73, 146, 325
Hermaphroditism; pseudohermaphroditism and adrenal disease, 333
Hinman, F.: Review of urologic surgery, 73, 146, 325
Hip: See also Femur
conditions involving hip joint, 166
dislocation, 169
fracture-dislocation of, 258
involvement in Gaucher's disease, 168
simplified surgical approach to, 144
von Hippel's Disease: See under Retina
Hopps, H. C.: Role of allergy in delayed healing and in disruption of wounds; antigenicity of catgut, 438
Role of allergy in delayed healing and in disruption of wounds; delayed healing and disruption produced by local allergic reaction (Auer phenomenon), 450
Role of allergy in delayed healing and in disruption of wounds; effect of specific sensitivity to catgut on reaction of tissues to catgut sutures and on healing of wounds in presence of catgut sutures, 445
Hospitals, naval casualties in base hospital in South Pacific, 305
Hueper, W. C.: Toxicopathologic studies on dye T-1824, 17
Humerus, fractures of, 229
Hydronephrosis, 328
Hypertension: See Blood pressure, high
Hypoproteinemia: See Blood, proteins

Ichniowski, C. T.: Toxicopathologic studies on dye T-1824, 17
Ileus: See Intestines
Industry, fractures of carpal scaphoid bone in industry and in military service, 278
Infection: See also Wounds; and under names of bacteria
vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; renal disease, neoplastic disease and infection, 193
Injections: See also Blood transfusion
intravenous administration of fat for nutritional purposes; experimental study, 395
Injuries: See Ankle; Nose; etc.
Instruments: See Apparatus
Internal Secretion: See Endocrine Glands
Intestines: See also Colon; Duodenum
Fistula: See Fistula
regional enteritis; pathologic study of 22 cases, 465
Islands of Langerhans: See Pancreas

Jaws, fractures of, 244
Jejunum: See Intestines
Johnson, H. F.: Fractures excepting fractures of neck of femur, 229
Johnson, M. L.: Traumatic retroperitoneal rupture of duodenum; presentation of case and review of literature, 372
Joints: See also under names of individual joints, as Elbow; Hip; etc.
Contracture: See Contracture
sprains, 98

Kamholz, J. H.: Effect of hypoproteinemia on susceptibility to shock resulting from hemorrhage, 491
Kidneys: See also Urinary Tract
abnormalities; renal ectopia, 325
actinomycosis of, 330
anomalous vessels, 74
anomaly, 73
calculi, 80
counterbalance, 80
cysts, 77, 329
Diseases: See also Hydronephrosis; Nephritis
diseases; renal lesions in von Hippel-Lindau disease, 352
diseases; vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; renal disease, neoplastic disease and infection, 193
foreign body in renal pelvis, 79
nephrotomy, 80
pyeloureteral changes in pregnancy, 81
renal hypertension, 329
renal operation for drainage of ascitic fluid, 330
rupture, 79
tumor, 75
Wilms's tumor, 327
Klein, W.: Oral administration of diethylstilbestrol for prostatism; clinical evaluation, 381
Knee: See Patella
Koontz, A. R.: Heat and mustard gas burns; comparison, 284
Kuhns, J. G.: Conditions involving shoulder and neck, 99

Lamont, E. S.: Reconstructive plastic surgery of absent ear with necrocartilage; original method, 53
Langerhans' Islands: See Pancreas
Laparotomy: See Abdomen
Lee, F. C.: Permeability of lymph vessels and lymph pressure, 355
Legs: See Extremities; Foot
Leonard, D. W.: Progressive gangrene in operative wound, 457
Leveridge, L. L.: Administration of succinylsulfathiazole before and after hemorrhoidectomy, 366
von Lichtenberg, A.: Review of urologic surgery, 73, 146, 325
Ligaments, Triangular: See Wrist
Ligatures: See Sutures
Lindau's Disease: See Angioma
Linton, R. R.: Two stage operation for carcinoma of transverse colon producing duodenocolic fistula; report of 2 cases, 197; correction, 371
Lion, K. S.: Apparatus for measuring rate of enzymatic digestion of absorbable surgical sutures and other protein fibers, 120
Lionello, J.: Pancreatic calculi; report of 7 cases in 2 of which cure was effected by pancreaticolithotomy, 137
Lips, cancer; chemosurgical treatment; microscopically controlled method of excision, 478
Liver, lobectomy; report of 3 cases, 267
results of long term experimental constriction of hepatic veins in dogs, 472
vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; hepatic disease, 185
Lobectomy: See under Liver
Loker, F. F.: Application of dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]) in trauma and gangrene, 1
Lymph, permeability of lymph vessels and lymph pressure, 355
Lymph Nodes, lateral aberrant thyroid; metastasis to lymph nodes from primary carcinoma of thyroid gland, 223
significance of supraclavicular signal node in patients with abdominal and thoracic cancer; study of 122 cases, 109
Lymphatic System: See also Lymph Nodes
permeability of lymph vessels and lymph pressure, 355

McNamee, H. G.: Effect of hypoproteinemia on susceptibility to shock resulting from hemorrhage, 491
Malakoplakia: See under Bladder
Malar Bone: See Zygoma
Mammary Gland: See Breast
Mandible: See Jaws
March Foot: See Foot
Fractures: See Metatarsus, fractures
Mediastinum, ganglioneuroma, 208
hemangioma; report of case, 126
Medicine, Military: See Military Medicine
Metatarsus: See also Foot
fractures, 236, 251
Metrazol, question of vertebral fractures in convulsive therapy and in epilepsy, 244
Military Medicine: See also Naval Medicine
compound fractures, 247
foot and military service, 92
fractures of carpal scaphoid bone in industry and in military service, 278
lesions of tendons, 171
Mohs, F. E.: Chemosurgical treatment of cancer of lip; microscopically controlled method of excision, 478
Montgomery, R.: Conditions of foot and ankle, 89
Muscles, scalenus anticus syndrome, 102
syphilis of tendon of long head of biceps muscle and of olecranon bursa, 423
Mustard Gas: See Gas

Narcosis: See Anesthesia
Nation, E. F.: Interstitial cell tumors of testis; report of 3 new cases, 415
Naval Medicine: See also Military Medicine
naval casualties in base hospital in South Pacific, 305
Navicular Bone: See Scaphoid Bone, Carpal
Neck, conditions involving shoulder and neck, 99
Negroes, progressive exophthalmos in toxic disease of thyroid gland; review of recent literature, with report of case of progressive post-thyroidectomy proptosis in 6 year old Negro girl, 214
Nephrectomy: See under Kidneys
Nephritis, 329. See also Albuminuria; Kidneys
Nephrotomy: See Kidneys
Nerves: See Nervous System; Paralysis
Nervous System, nervous regulation of clotting mechanism, 105
Nevi, giant nevus of thigh successfully treated by complete excision and primary grafting, 319
Newman, B.: Oral administration of diethylstilbestrol for prostatism; clinical evaluation, 381
Nipple: See Breast
Nose, injuries of, 246
Nutrition: See also Vitamins
intravenous administration of fat for nutritional purposes; experimental study, 395

Occupations: See Industry
O'Conor, V. J.: Review of urologic surgery, 73, 146, 325
O'Donoghue, D. H.: Fractures excepting fractures of neck of femur, 229
Old Age, oral administration of diethylstilbestrol for prostatism; clinical evaluation, 381
Olecranon: See Ulna
Operating Rooms: See Surgery
Orthopedic surgery, progress for 1942; preface, 266
progress for 1942; review prepared by editorial board of American Academy of Orthopaedic Surgeons, 89, 166, 229
Orthopedics: See Amputation; Fractures; etc.
Os Acromiale: See Scapula
Calcis: See Calcaneum
Centrale: See Wrist
Osgood-Schlatter Disease: See Tibia, tuberosity
Ossification: See also Bones, growth
centers, 179
Osteochondritis juvenilis, 168
Osteogenesis: See Bones, growth
Osteomyelitis complicating prostatic operations, 347
Osteoporosis: See Bones, atrophy
Owens, F. M., Jr.: Regional enteritis; pathologic study of 22 cases, 465

Pack, G. T.: Significance of supraclavicular signal node in patients with abdominal and thoracic cancer; study of 122 cases, 109
Pain: See under Shoulder
Palsy: See Paralysis
Pancreas, calculi; report of 7 cases in 2 of which cure was effected by pancreaticolithotomy, 137
Pancreaticolithotomy: See Pancreas
Paralysis, correction of opponens paralysis, 176
Volkmann's: See under Contracture
Patella, fractures of, 237
Pelvis: See also Gynecology
fractures of, 236
tilted, 168
Penicillin: See Gonorrhea
Penis, diseases; Peyronie's disease, 159
Peritoneum, traumatic retroperitoneal rupture of duodenum; presentation of case and review of literature, 372

Peyronie's Disease: See Penis, diseases
Phalanges: See Fingers and Toes
Pickrell, K. L.: Giant nevus of thigh successfully treated by complete excision and primary grafting, 319
Lobectomy of liver; report of 3 cases, 267
Plastic Surgery: See Surgery, plastic
Polycythemia vera; results of long term experimental constriction of hepatic veins in dogs, 472
Position: See Posture
Postlethwait, R. W.: Tuberculous abscess of thyroid gland; report of case and review of literature, 429
Posture, orthostatic albuminuria, 156
Pregnancy, pyeloureteral changes in, 81
Pringle's Disease: See Sclerosis, tuberous
Prostate, cancer, 149, 342
obstruction and diverticula of bladder, 149
oral administration of diethylstilbestrol for prostatism; clinical evaluation, 381
osteomyelitis complicating prostatic operations, 347
prostatectomy versus transurethral resection, 146
prostatitis, 150
recurrent symptoms after transurethral prostatectomy, 148
resection, 344
sarcoma, 344
Prostatectomy: See under Prostate
Prostatism: See Prostate
Prostatitis: See under Prostate
Prosthesis: See Breast; Testes
Proteins, apparatus for measuring rate of enzymatic digestion of absorbable surgical sutures and other protein fibers, 120
hypoproteinemia; clinical relationship of proteins and protein metabolism to therapy with reference to surgery, 36
in Blood: See Blood, proteins
Prothrombin: See Blood, coagulation
Pseudarthrosis, epiphyseal, 264
Pseudohermaphroditism: See Hermaphroditism
Pyelography; urography, 160
Pyuria: See under Urinary Tract

Races: See also Negroes
drepanocytosis (sicklemia) and apparently acute surgical condition of abdomen; report of their occurrence in white youth, with laparotomy, 123
Radium, ureteral injury by, 336
Radius, forearm reconstruction following partial resection of radius, 263
fractures of lower end of radius and ulna, 233
Ravdin, I. S.: Effect of hypoproteinemia on susceptibility to shock resulting from hemorrhage, 491
Regen, E. M.: Fractures excepting fractures of neck of femur, 229
Retina, renal lesions in von Hippel-Lindau disease, 352
Ribs, cervical, and scalenus anticus syndrome, 102
Richards, V.: Results of long term experimental constriction of hepatic veins in dogs, 472
Robbins, E. B.: Comparative value of some blood substitutes used for treatment of experimental shock, 315
Roentgen Rays, radiation injuries of bladder, 88
Therapy: See under names of organs, regions and diseases
Rowe, M. J., Jr.: Simplified surgical approach to hip, 144
Ryan, N. H.: Pancreatic calculi: report of 7 cases in 2 of which cure was effected by pancreaticolithotomy, 137

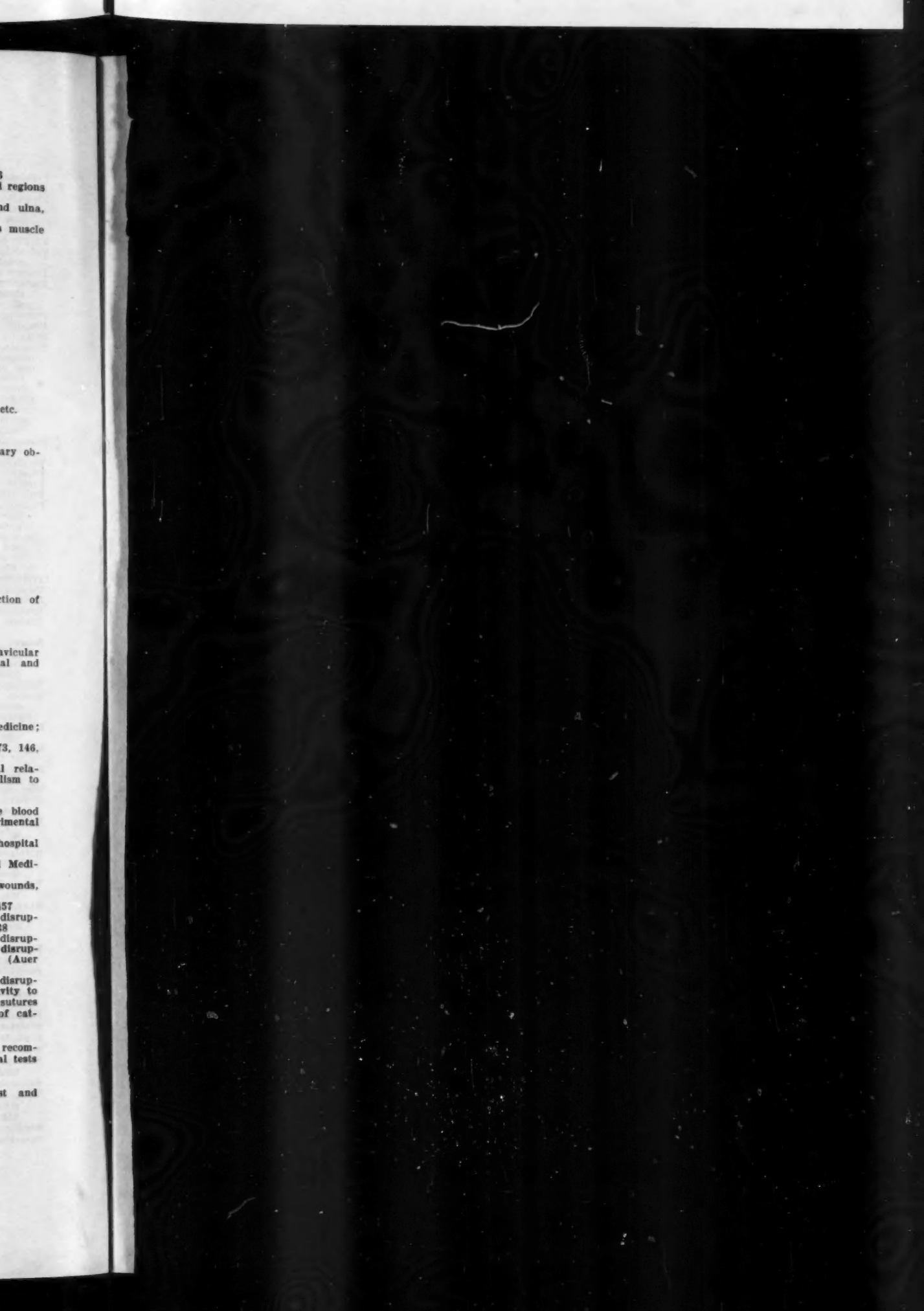
Sarcoma: See Cancer; Tumors; and under names of organs and regions, as Prostate; etc.
Scaphoid Bone, Carpal; fractures and dislocations of bones of hands and feet, 235
fractures in industry and in military service, 278
fractures of carpal navicular, 264
Scapula, anatomy and pathology, 99
Schistosomiasis, 341
Schlatter-Osgood Disease: See Tibia, tuberosity
Scholl, A. J.: Review of urologic surgery, 73, 146, 325
Schrager, V. L.: Syphilis of tendon of long head of biceps muscle and of olecranon bursa, 423
Sclerosis, tuberous, 327
Scott, C. C.: Comparative value of some blood substitutes used for treatment of experimental shock, 315
Scrotum, avulsion of, 350
Secretions, Internal: See Endocrine Glands
Semilunar Bone, fractures and dislocations of bones of hands and feet, 235
Senility: See Old Age
Sesamoid Bone: See Metatarsus
Sex, Intergrades: See Hermaphroditism
Shepard, D. V.: Mediastinal ganglioneuroma, 208
Shock, effect of hypoproteinemia on susceptibility to shock resulting from hemorrhage, 491
experimental, comparative value of some blood substitutes used for treatment of, 315
Shoulder: See also Clavicle; Humerus; Scapula
bilateral subluxation of acromioclavicular joint, 99
conditions involving shoulder and neck, 99
dislocation, 103
pain; treatment, 102
Sicklemia: See Anemia, sickle cell
Sizer, I. W.: Apparatus for measuring rate of enzymatic digestion of absorbable surgical sutures and other protein fibers, 120
Speed, J. S.: Fracture deformities, 259
Spermatic Cord, tumor, 351
Spine, fractures of, 242
question of vertebral fractures in convulsive therapy and in epilepsy, 244
Sponge rubber; prosthetic restorations for breast; technic using sponge rubber, 388
Sprains: See Ankles
Steindler, A.: Research, 178
Stuck, W. G.: Fractures excepting fractures of neck of femur, 229
Succinylsulfathiazole: See Sulfonamides
Sulfonamides, administration of succinylsulfathiazole before and after hemorrhoidectomy, 366
local application to synovial surfaces, 184
toxic reaction to administration of, 162
Suprarenals: See Adrenals
Surgery: See also Apparatus; Wounds; etc.
hypoproteinemia; clinical relationship of proteins and protein metabolism to therapy with reference to surgery, 36
plastic, bone and cartilage transplants, 262
plastic; reconstructive plastic surgery of absent ear with necrocartilage; original method, 53
progressive gangrene in operative wound, 457
role of allergy in delayed healing and in disruption of wounds; antigenicity of catgut, 438
role of allergy in delayed healing and in disruption of wounds; delayed healing and disruption produced by local allergic reaction (Auer's phenomenon), 450
role of allergy in delayed healing and in disruption of wounds; effect of specific sensitivity to catgut on reaction of tissues to catgut sutures and on healing of wounds in presence of catgut sutures, 445
vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; hepatic disease, 185
vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; renal disease, neoplastic disease and infection, 193
vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; thyroid disease, 190
Sutherland, R.: Simplified surgical approach to hip, 144
Sutures: See also under Surgery
apparatus for measuring rate of enzymatic digestion of absorbable surgical sutures and other protein fibers, 120
role of allergy in delayed healing and in disruption of wounds; antigenicity of catgut, 438
role of allergy in delayed healing and in disruption of wounds; delayed healing and disruption produced by local allergic reaction (Auer phenomenon), 450
role of allergy in delayed healing and in disruption of wounds; effect of specific sensitivity to catgut on reaction of tissues to catgut sutures and on healing of wounds in presence of catgut sutures, 445
Sympathicoblastoma, presacral, causing urinary obstruction, 353
Synovial Membrane, local application of sulfonamides to synovial surfaces, 184
Syphilis: See under names of organs and regions, as Tendons; etc.

T-1824: See Blood, volume; Evans Blue
Talus: See Astragalus
Tarsus: See Ankle; Astragalus; Calcaneum; Foot
Temperature: See Heat

Tendons, calcium deposits, 173
correction of opponens paralysis, 176
lesions of, 171
syphilis; syphilis of tendon of long head of biceps muscle and of olecranon bursa, 423
tendon ruptures about elbow, 170
Testes: See also Epididymis
abnormalities; polyorchidism, 350
interstitial cell tumors of; report of 3 new cases, 415
prosthesis, 350
tumor of epididymis and tunica vaginalis, 158
undescended; cryptorchidism, 157
Tetanus and gas gangrene, 313
Thiamine, vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; hepatic disease, 185
vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; renal disease, neoplastic disease and infection, 193
vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; thyroid disease, 190
Thigh: See also Hip
giant nevus of thigh successfully treated by complete excision and primary grafting, 319
Thompson, G. J.: Review of urologic surgery, 73, 146, 325
Thoracic Duct, permeability of lymph vessels and lymph pressure, 355
Thorax: See also Heart; Mediastinum; Ribs; etc.
penetrating wounds of chest, 311
significance of supraclavicular signal node in patients with abdominal and thoracic cancer; study of 122 cases, 109
Thrombosis, results of long term experimental constriction of hepatic veins in dogs, 472
tumor thrombosis of renal vein, 326
Thyroid, lateral aberrant thyroid; metastasis to lymph nodes from primary carcinoma of thyroid gland, 223
progressive exophthalmos in toxic disease of thyroid gland; review of recent literature, with report of case of progressive post-thyroidectomy proptosis in 6 year old Negro girl, 214
tuberculous abscess of; report of case and review of literature, 429
vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; thyroid disease, 190
Thyroidectomy, progressive exophthalmos in toxic disease of thyroid gland; review of recent literature, with report of case of progressive post-thyroidectomy proptosis in 6 year old Negro girl, 214
Tibia, fractures of, 238
tuberosity; Osgood-Schlatter disease, 406
Tissue: See also Cells
apparatus for measuring rate of enzymatic digestion of absorbable surgical sutures and other protein fibers, 120
role of allergy in delayed healing and in disruption of wounds; delayed healing and disruption produced by local allergic reaction (Auer phenomenon), 450
role of allergy in delayed healing and in disruption of wounds; effect of specific sensitivity to catgut on reaction of tissues to catgut sutures and on healing of wounds in presence of catgut sutures, 445
Toes: See Fingers and Toes
Torticollis, so-called congenital torticollis, 99
Tourniquet: See Hemostasis
Transplantation: See Grafts
Trauma, application of dicoumarin (3-3'-methylene-bis-[4-hydroxycoumarin]) in trauma and gangrene, 1
post-traumatic painful osteoporosis, 259
Trochanter: See Femur
Tubercle Bacilli, tuberculous bacilluria, 153
Tuberculosis: See also under names of diseases, organs and regions
tuberculous abscess of thyroid gland; report of case and review of literature, 429
Tumors: See also Angioma; Cancer; Ganglioneuroma; and under names of organs and regions, as Bladder; Epididymis; Kidneys; Testes; etc.
vitamin B_1 nutrition in surgical patients as determined by blood level of pyruvic acid; renal disease, neoplastic disease and infection, 193
Wilms: See under Kidneys
Tunica Vaginalis: See Testes

Uhry, E., Jr.: Osgood-Schlatter disease, 406
Ulcers: See also under names of organs and regions
tropical, 314
Ulna, fractures of lower end of radius and ulna, 233
syphilis of tendon of long head of biceps muscle and of olecranon bursa, 423
Ureterocele: See Ureters, dilatation
Ureterotomy: See under Ureters
Ureters: See also Urinary Tract
calculus, 82, 334
carcinoma, 334
dilatation, 82
injury by rachum, 336
injury during gynecologic operations, 335
intubated ureterotomy, 83
pyeloureteral changes in pregnancy, 81
spasm, 336
transplantation, 84
Urethra, caruncle, 151
diverticulum, 151, 349
periurethral extravasation, 150
Urinary Tract: See also Kidneys; Ureters; etc.
calculi, 352
infections of, 352
neurogenic conditions, 88
presacral sympathicoblastoma causing urinary obstruction, 353
pyuria, 151
sterile pyuria, 152
Urine, bacteria; tuberculous bacilluria, 153
suppression; anuria, 154
Urography: See Pyelography
Urolithiasis: See Urinary Tract, calculi
Urologic surgery, review of, 73, 146, 325

Vagina, Fistula: See Fistula
Vas Deferens; vasitis nodosa, 159
Veins: See also Thrombosis; etc.
Pressure: See Blood pressure
results of long term experimental constriction of hepatic veins in dogs, 472
tumor thrombosis of renal vein, 326
Venous Pressure: See Blood pressure
Vertebrae: See Spine
Viacava, E. P.: Significance of supraclavicular signal node in patients with abdominal and thoracic cancer; study of 122 cases, 109
Vitamins, B_1: See Thiamine
K: See Blood, coagulation
Volkmann's Contracture: See Contracture

War: See Military Medicine; Naval Medicine; Wounds; etc.
Wildbolz, E.: Review of urologic surgery, 73, 146, 325
Wilensky, A. O.: Hypoproteinemia; clinical relationship of proteins and protein metabolism to therapy with reference to surgery, 36
Wilms Tumor: See under Kidneys
Worth, H. M.: Comparative value of some blood substitutes used for treatment of experimental shock, 315
Wounded and Sick, naval casualties in base hospital in South Pacific, 305
Wounds: See also Military Medicine; Naval Medicine
casein in local treatment of burns and wounds, 130
progressive gangrene in operative wound, 457
role of allergy in delayed healing and in disruption of wounds; antigenicity of catgut, 438
role of allergy in delayed healing and in disruption of wounds; delayed healing and disruption produced by local allergic reaction (Auer phenomenon), 450
role of allergy in delayed healing and in disruption of wounds; effect of specific sensitivity to catgut on reaction of tissues to catgut sutures and on healing of wounds in presence of catgut sutures, 445
treatment of infection, 306
untoward effects of various substances recommended for burns or wounds; experimental tests on rats, 300
Wrist: See also Scaphoid Bone, Carpal
conditions involving elbow, forearm, wrist and hand, 169
surgery of, 171

Zygoma, fractures of malar bone, 246